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Asymmetric synthesis of substituted 2-aminotetralins

Thesis for the degree of Philosophiae Doctor

Trondheim, November 2010

Norwegian University of Science and Technology
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Jon Erik Aaseng

Trondheim, August 2010

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Preface

Presented in this thesis are the results obtained from the project: *Asymmetric synthesis of substituted 2-aminotetralins*. The initial goal was to establish new or improved routes to enantiopure 2-aminotetralin (2-AT) derivatives. The motivation for this project was based on the diverse applications various 2-ATs represent as biologically active compounds. Despite the role of 2-aminotetralins as interesting target molecules, reflected by the massive research activity in the field, no general and cost efficient route has really been established.

Chapter 1 in this thesis gives an introduction to 2-ATs as biologically active compounds, as well as a brief survey of the concepts of chirality and asymmetric synthesis. Aziridines are also presented, given their role as key intermediates in our developed strategies (chapters 2-4).

In chapter 2, a total synthesis of substituted (*S*)-2-ATs is presented, starting from natural L-aspartic acid. Two 2-AT derivatives were successfully synthesised, but especially one step (ring-closing to tetralones) proved difficult, providing up to 41% yield only.

Chapter 3 is directly based on the experiences we made in the former chapter, and presents an improved route from the same starting point (chiral pool strategy utilising L-aspartic acid). Again we struggled with one specific cyclisation reaction (up to 36% yield), but the remaining steps provided overall good yields.

In Chapter 4, a different approach has been targeted, i.e. asymmetric aziridination of 1,2-dihydronaphthalenes. Here, various copper, rhodium and ruthenium catalytic systems were tested with alternative nitrogen sources. While we were able to achieve quite good results for non-substituted 1,2-dihydronaphthalene, substituted substrates provided only mediocre yields and enantioselectivity. Aziridines were selectively ring-opened by catalytic hydrogenation to their respective *N*-protected 2-ATs in good yields.

Appended papers

I) Aaseng, J. E. and Gautun, O. R.
Synthesis of substituted (*S*)-2-aminotetralins via ring-opening of aziridines prepared from L-aspartic acid β-*tert*-butyl ester.
Tetrahedron, **2010**, *66*, 8982-8991.

II) Aaseng, J. E. and Gautun, O. R.
Synthesis of (*S*)-2-amino-7-methoxytetralin and isoindolo[1,2-a]isoquinolinone derivatives from L-aspartic acid.
Manuscript.

III) Aaseng, J. E., Melnes, S., Reian, G. and Gautun, O. R.
Asymmetric catalytic aziridination of dihydronaphthalenes for the preparation of substituted 2-aminotetralins.
Accepted for publication in *Tetrahedron*.

Abbreviations and symbols

$[\alpha]_D^{rt}$	optical rotation at room temperature (sodium D-line wavelength)
δ	chemical shift relative to standard (typically TMS)
Δ	heated to reflux temperature
2-AMT	2-aminotetralin
Asp	aspartic acid
Cbz	benzyloxycarbonyl
Boc	*tert*-butyloxycarbonyl
cap	caprolactam
COSY	correlated spectroscopy
DA	dopamine
DCC	N,N´-dicyclohexylcarbodiimide
DCE	dichloroethane
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DMAP	4-*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethyl formamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
ESI	electrospray ionisation
EWG	electron withdrawing group
F-C	Friedel-Crafts
FT-IR	Fourier-transformed infrared spectroscopy
HMBC	heteronuclear multiple bond correlation
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
5-HT	5-hydroxytryptamine
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
LA	Lewis acid
LiHMDS	lithium hexamethyldisilazan
MEPY	methyl 2-pyrrolidone-5-carboxylate
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
NOESY	Nuclear Overhauser Enhancement spectroscopy
Ns	nosyl, (*o*- or *p*-)nitrobenzenesulfonyl
Pf	phenylfluorene-9-yl
Phth	phthalyl
pK_a	acid dissociation constant
R_f	retention factor
rt	room temperature

SES	2-(trimethylsilyl)ethanesulfonyl
Tf	triflate, trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
Ts	tosylate, *p*-toluenesulfonyl

1 Introduction

1.1 Background

1.1.1 Chirality and asymmetric synthesis

Chirality is a fundamental property of three-dimensional objects. An object is chiral if it cannot be superimposed on its mirror image. In such cases, the two possible forms are referred to as enantiomers.[1] Chirality is of prime significance, as most biological macromolecules of living systems occur in nature in one enantiomeric form only. Like the natural L-amino acids, 19 of the 20 (one achiral) are chiral building blocks for proteins and enzymes.[2a] Likewise, sugars represent a group of natural compounds with well defined stereochemistry.[2b] The respective enantiomers of a biologically active chiral compound will interact differently with chiral receptors in organisms, with potentially dissimilar responses. For example, the natural amino acid (*S*)-aspargine is bitter, while its unnatural counterpart has a sweet taste.[3] And where one enantiomeric form of benzopyryldiol is considered to be highly carcinogenic, the other is inactive (examples demonstrated in Figure 1.1).[4]

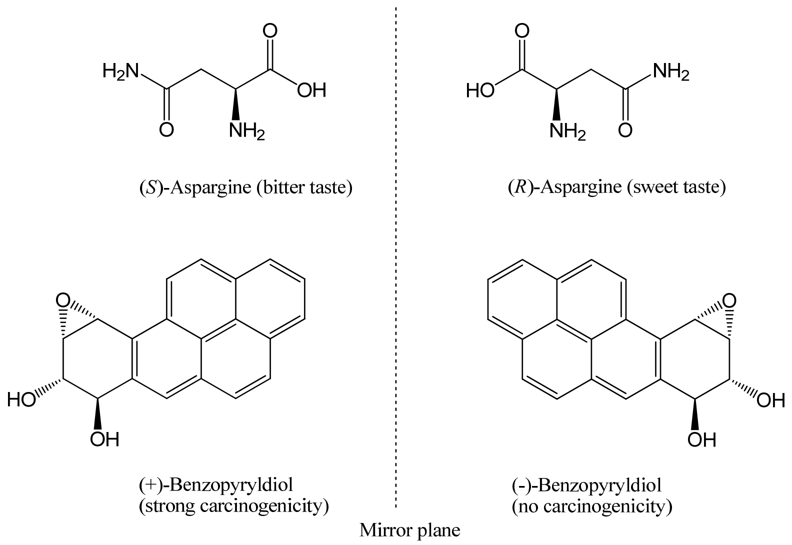


Figure 1.1: Examples of diverse enantiomeric characteristics

Keeping this in mind, it should be no surprise that chiral drugs today should be investigated and approved in the form of pure enantiomers, rather than as a racemic mixture. This is also one of the key reasons for the enormous effort that has been put into the development of new improved methods to synthesise enantiopure products, often referred to as *asymmetric synthesis*.

So – what is an asymmetric synthesis? There are various definitions present in the literature, e.g. the commonly quoted one by Marckwald,[5] and most appear to be quite cumbersome to state. This is mostly because of technical concerns regarding asymmetric induction and asymmetric reactions, as well as discussions about limitations. For the purpose of having a simplified and easy to handle definition, a representative textbook[6] uses the following: *An asymmetric synthesis is one which creates new stereogenic units in a controlled way*. The very same source also states that: *Nowadays, when we refer to asymmetric synthesis, we generally mean one which is capable of giving rise to enantiopure products*. Taking the latter statement into consideration, we might as well include classical resolution of racemic mixtures and chiral pool synthesis to the concept of asymmetric synthesis. However, looking back to the prior statement, no new stereogenic unit is really formed. Anyway, if we focus on the "true" and indisputable asymmetric syntheses, where new stereogenic units are created, they can be classified according to how the chiral influence is exerted:[7]

<u>I – Substrate-controlled methods (First-generation asymmetric synthesis)</u>

Diastereoselective reactions where the formation of a chiral centre is controlled by another chiral centre already present in the substrate.

<u>II – Auxiliary-controlled methods (Second-generation)</u>

Methods where a chiral auxiliary is covalently attached to the substrate and, through that, controls the asymmetric induction. This strategy, with intramolecular controlled induction, is basically the same in first- and second-generation methods. The difference is the attachment and removal of the auxiliary in the latter.

III – Reagent-controlled methods (Third-generation)

The formation of a new chiral centre is induced by a chiral reagent or catalyst, intermolecularly.

IV – Catalyst-controlled methods (Fourth-generation)

Catalytic modifications of the first-, second-, and third-generation methods tend to be considered together with this new fourth-generation. One general procedure involves a reaction of a chiral substrate with a chiral reagent, and is especially useful in reactions where two new stereogenic units are formed stereoselectively in one step. The most significant advance in asymmetric synthesis in the past three decades has however been the application of chiral catalysts capable of making chiral products from achiral substrates.

A simplified overview of the various generations of asymmetric synthesis is shown in Figure 1.2.

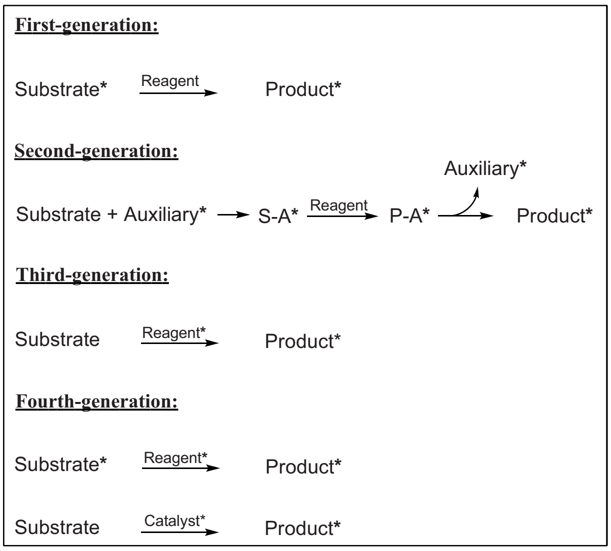


Figure 1.2: Generations of asymmetric synthesis (chirality displayed by *-symbol)

1.1.2 2-Aminotetralins- pharmacologically active compounds

Before the introduction of this class of compounds, we should discuss the basic structure of 2-aminotetralin. Tetralin might be considered as a partly hydrogenated naphthalene compound, where one ring is aliphatic and one is aromatic (Figure 1.3). Correct naming of such a ring system, according to IUPAC rules,[8] is in fact 1,2,3,4-tetrahydronaphthalene. Tetralin, however, is a common trivial name used in the literature.

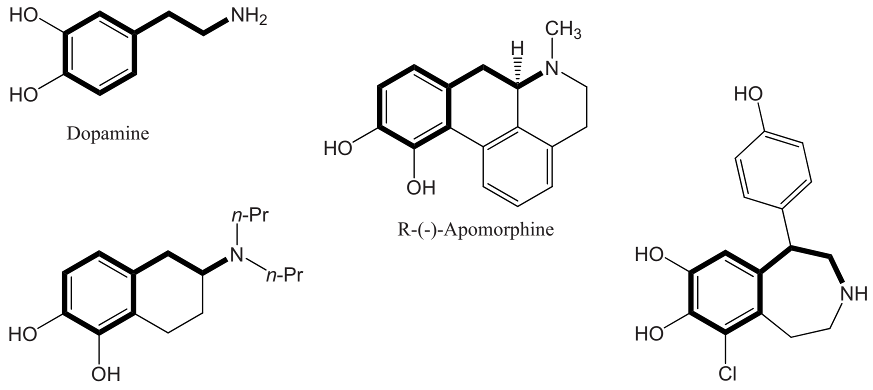
Tetralin or
1,2,3,4-Tetrahydronaphthalene

2-Aminotetralin (2-AMT) or
2-Amino-1,2,3,4-tetrahydronaphthalene

Figure 1.3: Tetralin and 2-aminotetralin, structures and IUPAC-names.

The pharmacological activity of 2-aminotetralin was first described by Bamberger and Filehne back in 1889.[9] Since then, a range of 2-aminotetralin (2-AMT) compounds have been found to possess pharmacological effects on the nervous system of the mammalian body, by binding selectively to serotonin (5-HT)[10-12] and dopamine (DA)[13-16] receptors, exerting agonist or antagonist activity. In several psychiatric diseases like anxiety, depression and schizophrenia, which are thought to be dysfunctions in the monoaminergic neuronal system, development of therapeutically useful 2-aminotetralins have emerged.[17-19] Various analogues are also known to show activity against adrenergic receptors[20] and antagonist activity at μ-opioid receptors.[21]

To emphasise the structural similarity between 2-AMTs and other compounds with similar activity, let's take a look at some well known dopamine agonists. Figure 1.4 demonstrates the structural resemblance between dopamine itself and three known agonists, including a specific 2-AMT derivative with well documented activity.[15,22,23] What they all have in common is a 2-phenylethylamine moiety (illustrated in bold), either in a conformational flexible structure, or as a part of a rigid multi-cyclic molecule.

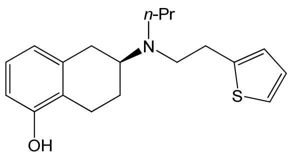


Dopamine R-(-)-Apomorphine *N*,*N*-Di-*n*-propyl-5,6-dihydroxy-2-AMT Fenoldopam

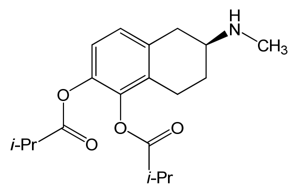
Figure 1.4: Dopamine and dopamine agonists

To highlight the importance and the diverse applications of 2-AMTs in the recent years, representative examples are shown in Figure 1.5.

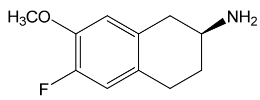
The chiral (*S*)-2-AMT drug *Rotigotine* is a non-ergotamine dopamine agonist, recently implemented in the treatment of Parkinson's disease.[24] The drug is delivered to the patient through transdermal patches, resulting in a constant level of dopamine in the blood and brain. This is considered to be a huge improvement compared to traditional levodopa pill treatment, which results in unfortunate fluctuation of the patient's dopamine level. Septic shock is a clinical syndrome which might occur from severe infections caused by bacteria, protozoa or by viruses. For the treatment, several 6,7-disubstituted 2-AMTs have been evaluated, and among them, especially racemic-2-amino-6-fluoro-7-methoxytetraline was found to be active.[25] Later studies have revealed that (*S*)-2-amino-6-fluoro-7-methoxytetraline is far more potent than the racemate.[26-28] Glaucoma, sometimes nicknamed "the sneak thief of sight", is a disease that affects the optic nerve. In the treatment, *N*-methyl-5,6-diisobutyroyloxy-2-AMT has been implemented.[29] Evaluation of the drug revealed that the (*S*)-enantiomer is about twice as selective as the racemate towards pre-synaptic α_2-adrenoceptors and dopamine D_2-receptors. A range of *N*-alkylated 2-amino-6,7-dimethoxytetralins have demonstrated pharmacological activity as antihypertensive agents. However, the activity tests reported in the literature only refer to racemates in this context.[30] In the treatment of obesity, amphetamines have been enlisted for the purpose of inducing weight loss, but undesirable side effects have led to search for more specific dopamine agonists.[31] Various 2-AMTs, especially their *S*-enantiomers, have been evaluated for this purpose. Among these, derivatives of (*S*)-2-amino-7-methoxytetralin have been applied as active compounds in diet pills.[32]



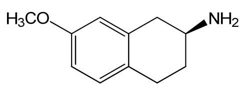
Rotigotine
in Parkinson's disease treatment



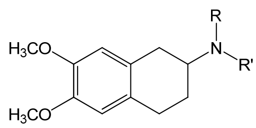
(*S*)-*N*-Methyl-5,6-diisobutyroyloxy-2-AMT
in opthalmic disorder (Glaucoma) treatment



(*S*)-6-Fluoro-7-methoxy-2-AMT
in septic shock treatment



(*S*)-7-Methoxy-2-AMT
Appetite suppressant in diet pills



N-alkylated 6,7-dimethoxy-2-AMT
Antihypertensive agents

Figure 1.5: Examples of pharmacologically active 2-AMTs used in various treatments

In an *in vivo* study of the respective enantiomers of *N*,*N*-di-*n*-propyl-5-hydroxy-2-AMT, it was discovered that the *S*-enantiomer is a very potent D_2-receptor agonist. On the other hand, the *R*-enantiomer was found to be a weakly potent antagonist.[33]

To summarise according to the examples above (Figure 1.5), it appears to be a general preference for the *S*-enantiomer of 2-AMTs when concerning their pharmacological activity. But in some cases, no enantiomeric preference has been discovered, or even studied, thus racemic mixtures are utilised. On the other hand, there are indeed a few striking examples of a strong preference for the specific *R*-(+)-2AMT enantiomer. One example is the very potent serotonin 5-HT_{1A} agonist (*R*)-(+)-*N*,*N*-di-*n*-propyl-8-hydroxy-2-AMT (8-OH-DPAT), which has become the ligand of choice in binding experiments within this receptor subclass.[34] Another example is (*R*)-(+)-*N*,*N*-di-*n*-propyl-7-hydroxy-2-AMT (7-OH-DPAT), which has been found to be a highly selective dopamine D_3 -ligand.[35] As a conclusion, we might say that these examples underscore the importance of synthesising such compounds in their pure enantiomeric form.

1.1.3 Aziridines as key intermediates

Since aziridines play a crucial role as key intermediates in the strategies presented in this thesis, a brief introduction is given herein.

Structure, physical and biological properties

Aziridines are structural units consisting of a three-membered nitrogen heterocycle with an amino group and two methylene groups. The bond angles in the ring are approximately 60º, which is much less than the regular 109.5º angle in sp^3-hybridised hydrocarbons. This is comparable to epoxides and cyclopropanes, which also share this strained three-membered ring structural characteristic (Figure 1.6).[36]

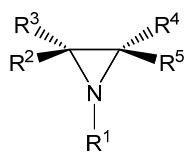
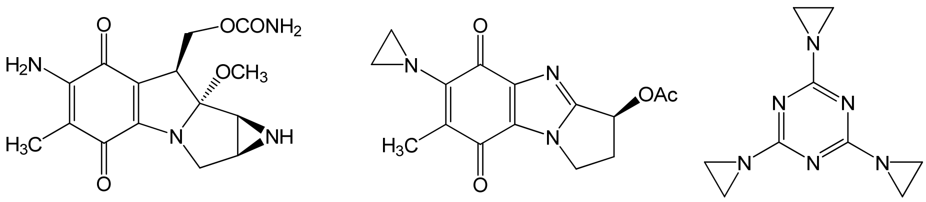


Figure 1.6: The general structure of aziridines

The bonds are considered to be somewhat bent, and thereby also known as “banana bonds”. To assume this strained structure, an increase in the p-character is needed for the ring bonds, with the consequence of a higher degree of s-character on the C-R bonds, hence making them shorter.[37] The angle strain in aziridines also results in higher energy barriers for nitrogen inversion, i.e. pyramidal (or “umbrella”) inversion, which is extremely rapid in flexible aliphatic amines. As a result, stable aziridine invertomers can actually be physically separated in special cases.[38] Interestingly, this particular motion has recently also been investigated for the purpose of developing molecular switches in nanoscale devices.[39] The structural consequence of the ring also results in lowered basicity of aziridines compared to aliphatic amines, which is due to the increased s-character for the nitrogen lone pair in aziridines (aziridine pK_{aH} 7.9[40] and e.g. diethylamine pK_{aH} 10.9[41]).

Aziridines occur in several natural products which have been found to possess valuable properties in medicinal chemistry. Mitosanes (Mitomycins) are a well known class of compounds that demonstrates anticancer and antibiotic effects.[42,43] Two other families of anticancer natural products are Azinomycins[44,45] and the PBI (pyrrolo[1,2-a]benzimidazole) class.[46] Examples of synthetic aziridines with similar properties are triethylenemelamine (anticancer)[47,48] and 1-alkoxy-2-aziridinephosphonates (antibiotic).[49] The structures of some of these biologically active aziridines are shown in Figure 1.7.



Mitomycin C **PBI-A** **Triethylenemelamine**

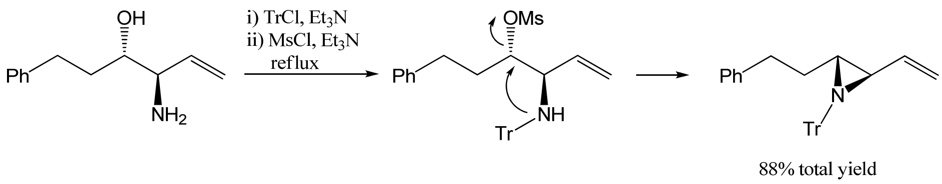
Figure 1.7: Biologically active aziridines with anticancer properties

Synthesis of aziridines

During the last decades, several review articles concerning aziridine synthesis have emerged.[50-53] One way of classifying these reactions are by their respective precursors. Three major classes of precursors are presented below, illustrated with specific examples:

I) From 1,2-amino alcohols (Wenker type synthesis[54])

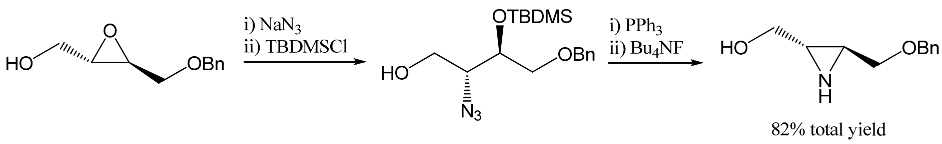
By converting the hydroxyl group into a good leaving group (typically sulfonates), the amine lone pair or the amide anion can cause an intramolecular displacement reaction. A specific two step procedure is shown below (Scheme 1.1), demonstrating the synthesis of a vinylaziridin.[55]



Scheme 1.1

II) From epoxides (azide ring opening and Staudinger reduction)

Ring opening reactions of epoxides with an azide followed by a Staudinger reduction[56] with triphenylphosphine proceeds via different intermediates to aziridines. A specific example published by Tanner and Somfai[57] is shown in Scheme 1.2:

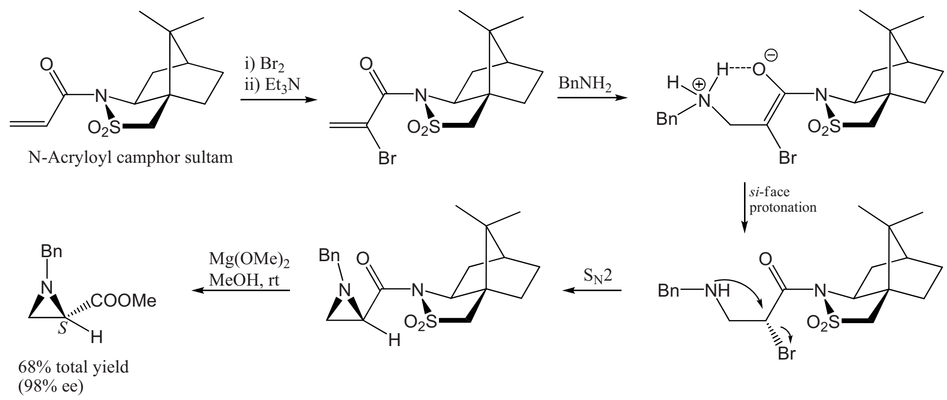


Scheme 1.2

III) From alkenes (nitrene addition or the Gabriel-Cromwell reaction)

Asymmetric aziridinations via nitrene transfer to alkenes, by means of transition metal catalysts, will be thoroughly presented in Chapter 4.

A range of chiral derivatives of α-bromoacrylates undergo reactions with amines to yield chiral aziridines. An example of this auxiliary mediated diastereoselective Gabriel-Cromwell reaction is presented below (Scheme 1.3).[58]

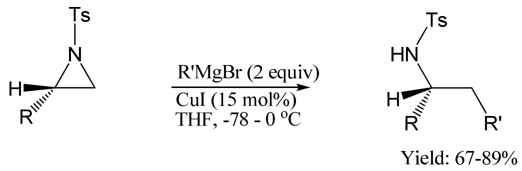


Scheme 1.3

Ring-opening reactions

The ability of aziridines to undergo highly regio- and stereoselective ring-opening reactions makes them interesting synthetic building blocks with great synthetic value.[59-61] Numerous nucleophiles can successfully perform such reactions. Only a brief introduction to carbon nucleophiles will be given here based on their relevance for this project.

Ring-opening of aziridines by carbanion species results in the formation of new carbon-carbon bonds and, through that, considerable attention has been attracted.[59] Aziridines are considered to be relatively non-reactive electrophiles, and require activation to perform ring-opening reactions with good regio- and stereo control.[60] Activation is performed by the introduction of an electron withdrawing group (EWG) on the aziridine nitrogen, and thereby giving rise to stabilisation of the negative charge present in the transition state. This is primarily due to the inductive effect, but with *N*-carbonyl substituents, a thermodynamic resonance stabilisation of the intermediate anion also contributes.[51] Examples of such EWG-groups, which also serve as amine protective groups are acyl, carbamate or sulfonate functionalities. Among the various alkyl metal reagents used in these reactions, soft organocopper species have very often been preferred since they tend to provide good chemoselectivity.[62-64] Hard organolithium and organomagnesium (Grignard) reagents have also been reported to work satisfactory in some cases.[65-67] However, they are considered to be less chemoselective and are, due to their higher reactivity, more prone to react with the protecting group or other substituents present in the substrate. In a representative example below, various tosyl protected aziridines are regioselectively ring opened (Scheme 1.4).[68]



R = Bn, *i*-Pr, Me
R' = Ph, 4-MeOPh, 2-MeOPh, 2-thiophene, 3-thiopene, 3-benzothiophene, 1-naphthyl

Scheme 1.4

Application of Lewis acid catalysis broadens the scope even more. Examples for selective ring-opening reactions of non-activated aziridines with Gilman cuprates (R_2CuLi), catalysed by BF_3-etherate, have been reported.[69]

1.2 Objectives and strategies of this project

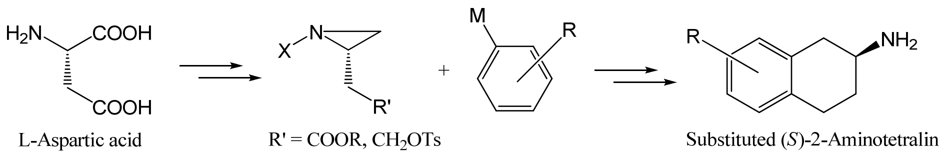
The literature concerning 2-aminotetralin derivatives is massive[70] and the main reason for this can be explained by the diversity this class of compounds represents. As active agent in various drugs and therapeutic remedies, pharmaceutical companies require efficient and reliable methods for their production. And obviously – with cost efficiency as a key factor as well.

In this project, our objective was to improve or design methods to synthesise enantiopure 2-aminotetralins. The methods were also designed with the intension to be relatively general, and capable of synthesising several analogues of substituted 2-aminotetralins.

Two main approaches towards enantiopure 2-aminotetralins have been targeted in this project:

Chiral pool approach

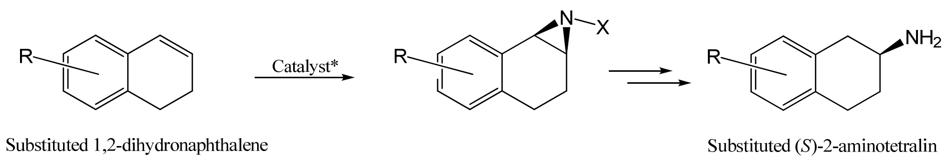
The cheap and readily available L-aspartic acid was chosen as the chiral source (Scheme 1.5). In chapters 2 and 3, the results of two different total syntheses of substituted (*S*)-2-aminotetralins are presented. These chapters have served as basis for two papers (Paper I and II for chapter 2 and 3, respectively).



Scheme 1.5

Asymmetric catalysis approach

Preparation and testing of new catalytic systems for catalysing asymmetric aziridinations of alkenes (1,2-dihydronaphthalenes) has been attempted (Scheme 1.6). The results are presented in chapter 4, as well as in Paper III.



Scheme 1.6

Each chapter initially presents relevant background information, covers relevant knowledge and presents the current status in the specific areas. Finally, a summary of the results is given with some comments on the potential and future perspectives.

2 Chiral pool synthesis of 2-aminotetralins– Part I

2.1 Background

In this chapter we present a brief overview of the main synthesis of 2-aminotetralins known from the literature.

Optical resolution

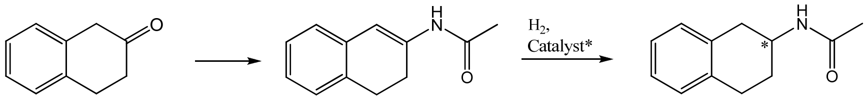
Several examples of resolution of various precursors in the synthesis of enantiopure 2-aminotetralins have been reported.[71-73] Resolution of racemic 2-aminotetralins is also well documented.[74,75]

Chemoenzymatic synthesis

Through various chemoenzymatic protocols (*R*)-8-methoxy-2-AMT[76] and (*S*)-7-methoxy-2-AMT[77] have been successfully produced. In a publication by Martin and co-workers, aminotransferases are utilised in the synthesis of enantiopure 2-aminotetralins.[78]

Catalytic hydrogenation of enamines, enamides and ene carbamates

Another common synthetic route to 2-aminotetralins starts from β-tetralones. By reacting them with amines or amides, followed by a subsequent dehydration step, enamines or enamides are formed, respectively (for example of the latter, see Scheme 2.1). Catalytic hydrogenation of such systems results in racemic 2-aminotetralins, which have been known for several decades.[79] Since the turn of the millennium, a range of chiral hydrogenation catalysts have been reported to produce enantioenriched 2-aminotetralins. However, very often low conversion and/or low to mediocre enantioselectivity was obtained. Most of these chiral catalysts are either ruthenium[80-82] or rhodium[83-85] based, and a broad range of ligands have been investigated. As the common benchmark substrate, *N*-(3,4-dihydro-2-naphthalenyl)acetamide has often been chosen in the evaluation of these asymmetric hydrogenations (Scheme 2.1).



β-Tetralon *N*-(3,4-dihydro-2-naphthalenyl)acetamide *N*-(1,2,3,4-tetrahydro-2-naphthalenyl)acetamide

Scheme 2.1

Exceptionally good results for this transformation have been obtained through recent advances in supramolecular catalysis.[86] The benchmark reaction (Scheme 2.1) was shown to proceed with full conversion and high enantioselectivity (94% ee) by applying a specific supraphos ligand (Figure 2.1). The authors of this publication point out the importance of a large library screening, which in their case resulted in only one successful out of 64 supraphos ligands tested.

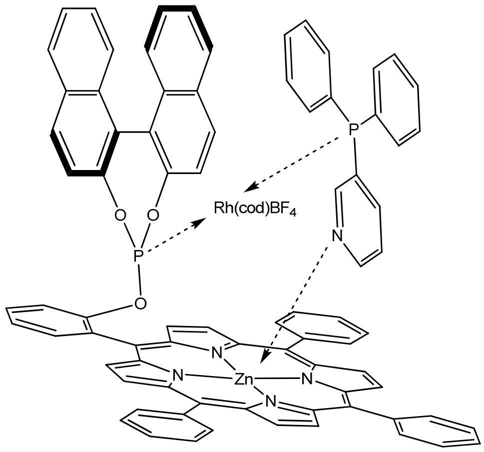
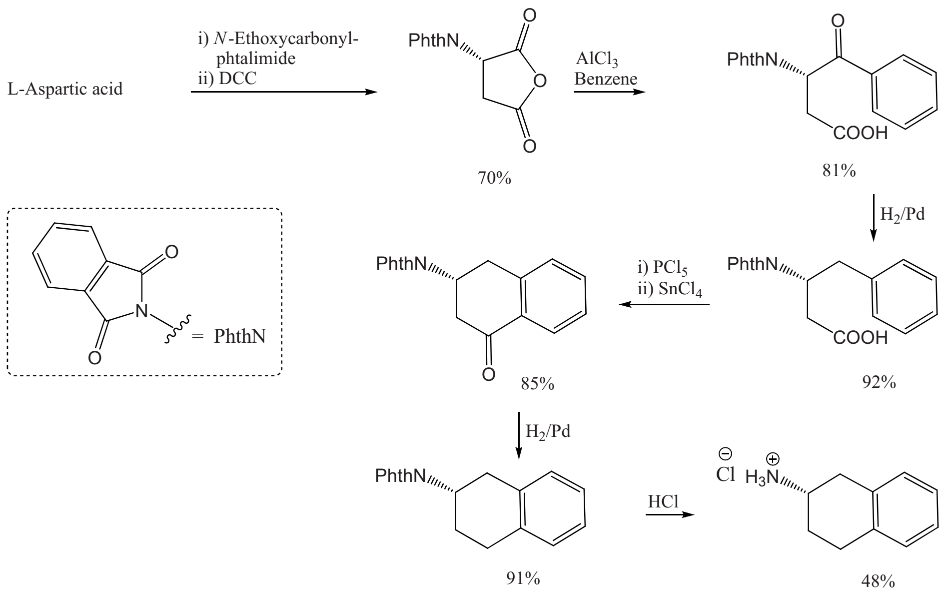


Figure 2.1: Construction of the successful rhodium catalyst with bidentate supraphos ligand. The nitrogen donor atom reversibly coordinates to zinc, and thereby creates the bidentate supraphos ligand, which in turn can coordinate to the rhodium metal.

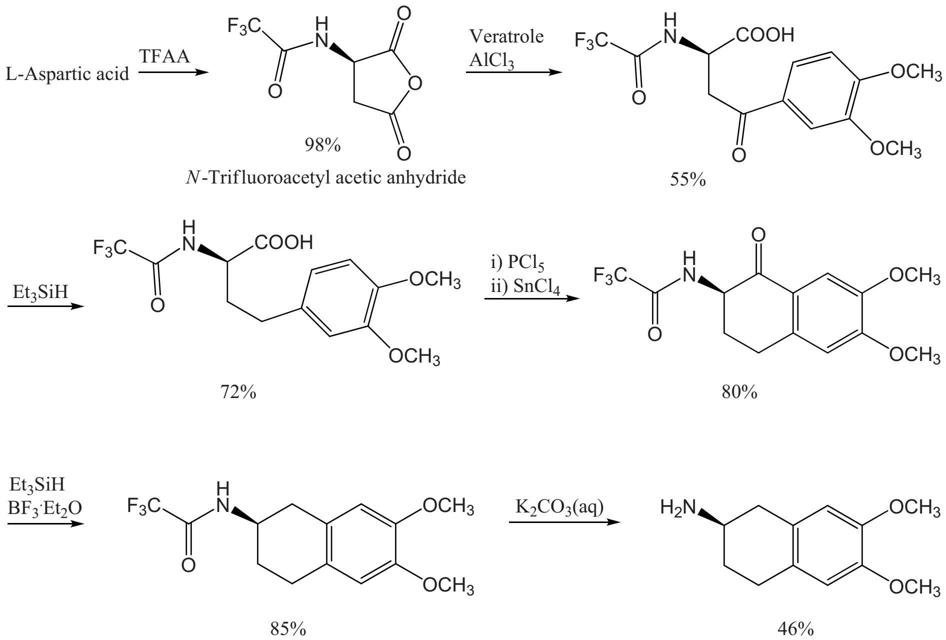
Chiral pool synthesis from natural amino acids

In a recent publication by Quiclet-Sire and co-workers, L-phenylalanine and L-tyrosine serve as chiral building blocks in the synthesis of rare 4-substituted 2-aminotetralins.[87] Utilisation of L-aspartic acid has also previously been reported.[88,89] The basis for this strategy is the formation of an *N*-protected aspartic anhydride derivative. This cyclic anhydride is prone to react with a nucleophilic aryl compound, catalysed by a Lewis acid. Followed by a sequence of reductions, cyclisation and *N*-deprotection, 2-aminotetralins are produced. In the earliest example, published by Zymalkowski and Dornhege, a phthalyl group serves as the *N*-protecting group (Scheme 2.2).[89]



Scheme 2.2

In a procedure published by Nordlander and co-workers (Scheme 2.3),[88] a trifluoroacetic anhydride is initially formed as the chiral synthon (method published earlier by Lapidus and Sweeney [90]).

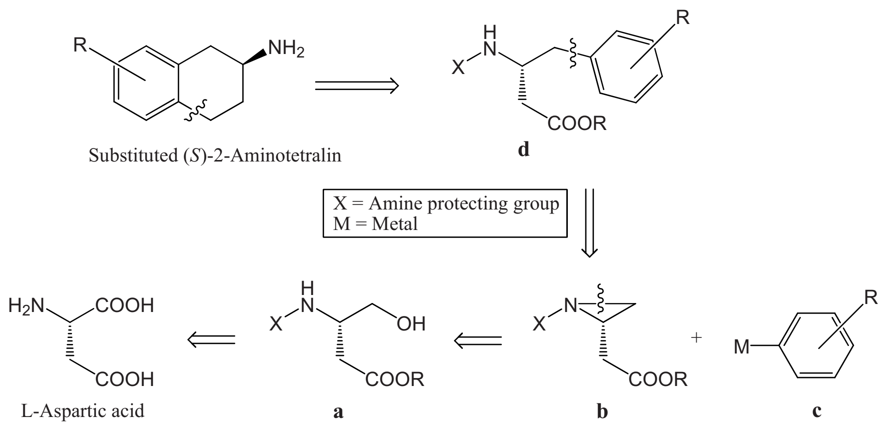


Scheme 2.3

This methodology has served as the basis for a range of analogues, described in various patents and publications, which all utilise the *N*-trifluoroacetyl aspartic anhydride as the starting point.[28,91-93]

2.2 Retrosynthesis and target molecules

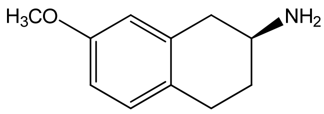
In our attempt, we investigated the possibility of making an appropriate *N*- and *C*-protected aziridine as the key intermediate, which could in turn be regioselectively opened by an aryl nucleophile. The strategy of our synthesis was based on the retro-synthetic approach described in Scheme 2.4.



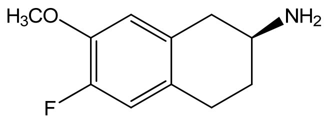
Scheme 2.4

Initially, protection of the β-carboxylic acid and the amino group of L-aspartic acid should be performed. Then a reduction to an amino alcohol (**a**) makes the starting point in the transformation to aziridine (**b**). The key step, where the two synthons (**b** and **c**) are brought together, is the regioselective ring-opening of the protected aziridine (**b**) with an appropriate aryl nucleophile (**c**), resulting in the ring-opened product (**d**). In the final steps, an intramolecular cyclisation followed by a deoxygenation should then provide the 2-aminotetralins.

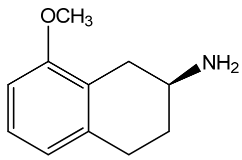
With the goal to accomplish a general synthetic route, we decided to aim for four target molecules (**27**-**30**), differing only in the aromatic substituent pattern. As a consequence, the aryl reagent becomes the only variable for the reaction with the enantiopure aziridine. The specific target molecules **27**-**30** (Figure 2.2) were all chosen among the analogues relevant for pharmaceutical industry, i.e. molecules which are known to exert biological activity (see Chapter 1.1.2).



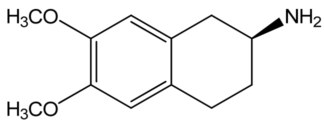
(*S*)-2-Amino-7-methoxytetralin (**27**)



(*S*)-2-Amino-6-fluoro-7-methoxytetralin (**28**)



(*S*)-2-Amino-8-methoxytetralin (**29**)



(*S*)-2-Amino-6,7-dimethoxytetralin (**30**)

Figure 2.2: Target molecules

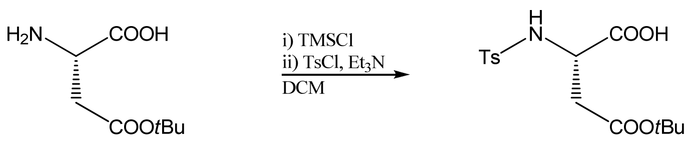
The results from this work are described in the following chapter.

2.3 Results and discussion

2.3.1 Aspartic acid protecting groups

A selective protection of the β-carboxylic acid function of aspartic acid was required for the synthetic strategy. After some considerations, the protection group of choice became the *tert*-butyl ester. The bulky *tert*-butyl substituent not only protects the carbonyl moiety against nucleophilic attack, but also demonstrates resistance towards basic hydrolysis.[94a] Aspartic acid 4-*tert*-butyl ester (**1**) is commercially available, but it can also be synthesised through various protocols from cheap and readily available L-aspartic acid, through e.g. esterification of its boron trifluoride complex.[95]

Protection was also necessary for the amine function to suppress its nucleophilic character and to prevent racemisation during the course of the reaction.[94f] This protection group also needed to be stable under basic reaction conditions. Based on these requirements, three candidates were considered: *tert*-butyloxycarbonyl (Boc), benzyloxycarbonyl (Cbz) and *p*-toluenesulfonyl (Ts). The two former are well known in peptide synthesis, among others for their ability to suppress racemisation.[94f] Introduction of a Boc or a Cbz protective group is straightforward, and deprotection can easily be achieved by acidolysis or catalytic hydrogenation, respectively.[94b-c] Compared to these two, the tosyl group is a more robust candidate, stable in both basic and acidic environment.[94e] The disadvantage of using *N*-tosylates is related to the deprotection step, where one-electron transfer reagents are required. Synthesis of *N*-tosylate **2b** is presented in Scheme 2.5, while carbamates **2a** and **2c** are commercially available and were purchased.

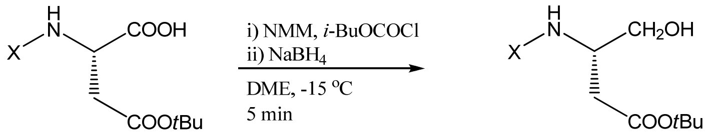


1 **2b** (84% yield)

Scheme 2.5

2.3.2 Reduction to amino alcohols

The reduction of the acids **2a-c** were performed by a protocol involving a mixed anhydride intermediate as the objective of the sodium borohydride reaction.[96] The isolated yields were typically in the range of 70–90% (Scheme 2.6 and Table 2.1), with the exception of acid **2b**. The obvious advantages of this method were the very short reaction time and the mild reaction conditions.



2a-c **3a-c**

Scheme 2.6

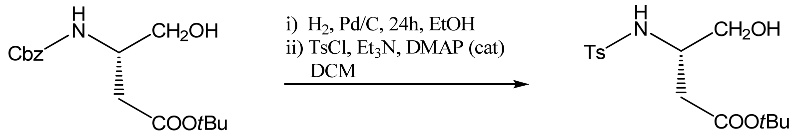
Table 2.1: Reduction via mixed anhydride intermediate

Entry	X	Acid	Alcohol	Yield (%)
1	Cbz	**2a**	**3a**	89
2	Ts	**2b**	**3b**	-[a]
3	Boc	**2c**	**3c**	78

a) Reduction of **2b** failed to provide alcohol **3b**.

An efficient reduction of **2b** failed to succeed under these conditions. Attempts with alternative solvent (DMF) or elevated temperature (room temperature), were also unsuccessful. Reduction by a combined sodium borohydride/iodine protocol, failed as well.[97] Another rather sophisticated derivatisation attempt, involving the reduction of a benzotriazole intermediate, was also investigated. The substrate was synthesised according to Katritzkys protocol,[98] and subsequently reduced according to Nain Singh and Kaur[99] resulting in approx 20% yield of **3b**. The reason for the low yield was primarily due to difficulties in the formation of the acylbenzotriazole substrate, and not the reduction itself. Borane reductions of **2b** also proved to give low yields (<25%), even by using as much as 6 equivalents of the reducing agent. As a comparison, Stanfield and co-workers reported good yields (75-90%) for a series of Boc-protected amino acids by this methodology.[100]

An alternative attempt to achieve alcohol **3b** in an acceptable yield was performed by a deprotection–reprotection sequence from alcohol **3a**. Catalytic hydrogenation over Pd/C and subsequent *N*-tosylation afforded the amino alcohol **3b** in a total yield of 84% (Scheme 2.7).



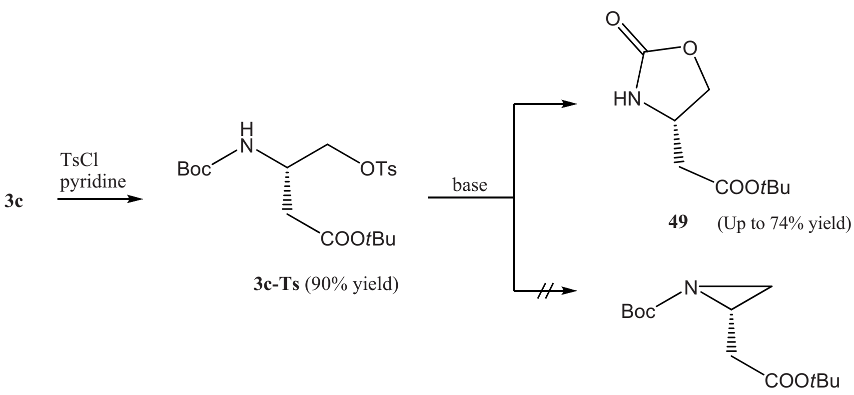
3a 3b (84% yield)

Scheme 2.7

Inspired by the fact that selective tosylation of the intermediate amino alcohol (Scheme 2.7) reacted smoothly and provided a good yield, we decided to investigate the possibility of reducing ester **1**, prior to *N*-protection. A borane/BF_3-protocol for the reduction of L-valine to L-valinol was tested, but it proved to be destructive for the *tert*-butyl ester function.[101]

2.3.3 Ring-closing reactions to aziridines

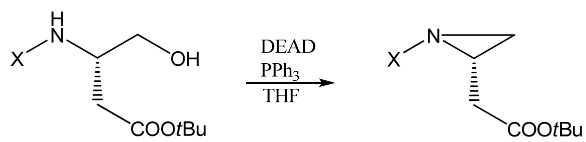
Our first consideration in the aziridine syntheses was to utilise a typical Wenker-type substrate,[54] i.e. derivatisation of the alcohol function with a good leaving group. Initial attempts were performed by tosylation of *N*-Boc-amino alcohol **3c** to tosylate **3c-Ts**.[102] However, this compound failed to react to aziridine **4c** when treated with various bases (Et_3N, 2,4,6-dimethylpyridine, LiHMDS, NaH), and instead we observed the formation of oxazolinone **49** (Scheme 2.8).



Scheme 2.8

Formation of oxazolinones from tosylated (or mesylated) *N*-Boc-β-amino alcohols, have previously been reported in the literature.[103,104] This is also in accordance with the conclusion from Nakajima and co-workers, who reported oxazolinone formation as the major product from a range of *O*-tosylated *N*-acyl and *N*-carbamoyl protected amino alcohols.[105] In a relevant example by Song and co-workers, compound **3a** was mesylated under basic (diisopropylethylamine) conditions, but no aziridine **4a** was reported to be formed.[106]

Based on these results we decided to terminate this ring-closing strategy and turned our attention to the Mitsunobu-reaction,[107,108] where several successful aziridination reactions have been reported.[109-111] The advantages of this reaction are the mild reaction conditions, the short reaction times and the fact that it is a simple one-pot transformation. Aziridination of amino alcohols **3a-c** was tested under various reaction conditions, utilising the classical diethyl azodicarboxylate (DEAD)/triphenylphosphine reagents (Scheme 2.9 and Table 2.2).



3a-c **4a-c**

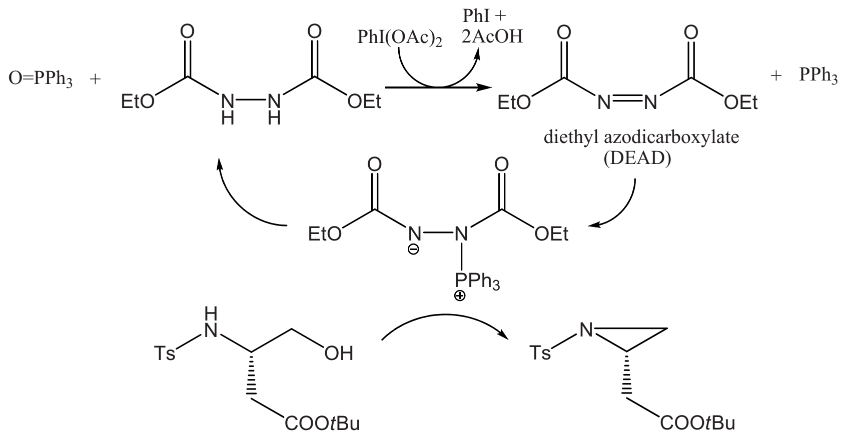
Scheme 2.9

Table 2.2: Aziridination under Mitsunobu-conditions

Entry	X	Amino alcohol	Aziridine	Yield (%)
1	Cbz	**3a**	**4a**	71[a]
2	Ts	**3b**	**4b**	90[a]
3	Boc	**3c**	**4c**	46[b]

a) 1.0 equiv DEAD/PPh_3, 0 ºC, 5-6 h. b) 2.0 equiv DEAD/PPh_3, rt, 1-2 h.

A well known drawback concerning the Mitsunobu-reaction is the purification step. For many relatively polar products, it may be difficult to remove diethyl hydrazine dicarboxylate derivatives as well as triphenylphosphine oxide completely. Recent advances concerning the Mitsunobu-reaction have been dealing with this, and successful attempts to perform the Mitsunobu-reaction with catalytic amounts of DEAD have been reported.[112] The catalytic cycle works by using a stoichiometric amount of iodosobenzene diacetate (hypervalent iodine) as an oxidant for the hydrazine derivative. By utilising such a system, easily removable iodobenzene and acetic acid are formed together with triphenylphosphine oxide. The reported test system was an intermolecular esterification reaction (2 mmol scale) with 4-nitrobenzoic acid and 2-phenylethanol, yielding up to 90% of the products.

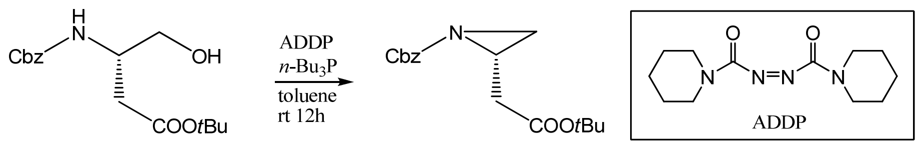


3b **4b**

Scheme 2.10

Inspired by the catalytic Mitsunobu-reaction, we decided to apply the reaction conditions to our intramolecular aziridination reaction (Scheme 2.10). Cyclisation of amino alcohol **3b** was attempted because of the substrates high performance in the stoichiometric reaction (entry 2, Table 2.2). However, when the reaction was performed in a 0.3 mmol scale, only a stoichiometric amount of product **4b** (based on DEAD) was isolated, indicating no catalytic effect.

An alternative to the classical DEAD/triphenylphosphine-reagent in Mitsunobu-reactions is the 1,1'-(azodicarbonyl)dipiperidine (ADDP)/tributylphosphine (TBP)-system.[113] While the former method required sufficiently acidic substrates (pK_a <11) to react (corresponds to X-NH-R acidity for **3a-d**), the latter is reported to work even for less acidic groups (pK_a 13). The difference in reactivity has been explained by three factors:[113] i) Increased nucleophilicity of the applied phosphine (smaller substituents in PBu_3 than PPh_3). ii) Higher degree of positive charge on phosphorous in the intermediates (no aromatic delocalisation). iii) Intermediate azo-anion, responsible for the deprotonation of the acid, is more basic. To investigate if the ADDP/TBP-system is capable of improving the yield, we decided to test amino alcohol **3a** (predicted pK_a (H_2O) = 11.33 ± 0.46)[114] (Scheme 2.11). The isolated yield of *N*-Cbz-aziridine **4a** was found to be 28%, which did not show any improvement compared to the previous attempts. Since both, **4a** and **4b,** were formed in good yields by the DEAD/PPh_3-system, we decided not to pursue any optimisation work.



3a **4a** 28% yield

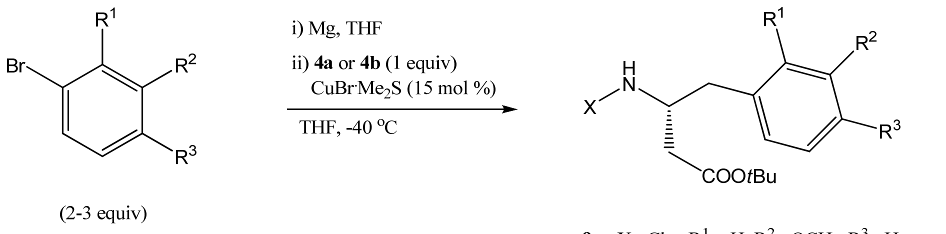
Scheme 2.11

2.3.4 Regioselective ring-opening of aziridines

After an evaluation of the two alternative carbamate protection (Cbz and Boc) strategies, we decided at this point to focus *only* on Cbz protected substrate **4a** in the following part of the developing strategy. Based on this, Cbz-aziridine **4a** and Ts-aziridine **4b** were chosen as substrates for the reaction with the various aryl nucleophiles. Both of them are considered to be activated aziridines, due to the EWG-substituents on the nitrogen atom.

For the synthesis of the four target molecules, we purchased the following substituted bromobenzenes: 3-bromoanisole (**5**), 5-bromo-2-fluoroanisole (**6**), 2-bromoanisole (**7**) and 4-bromoveratrole (**8**).

Initial reactions quickly revealed that stoichiometric control of the Grignard-reagent was crucial. To ensure controlled reaction conditions for the envisioned ring opening reactions, we needed a system for quantifying the Grignard-reagent. To do this, we implemented the protocol developed by Love and Jones, where salicylaldehyde phenylhydrazone is used as a titration indicator.[115] Before the addition of freshly prepared Grignard-reagent to the aziridines, the concentration was determined by titration (typically 1.0-1.1 M). The results of the reactions between aziridine **4a** and **4b** and the four respective Mg-organyls of **5-8**, are presented in Scheme 2.12 and Table 2.3:



5: R^1 = H, R^2= OCH_3, R^3= H
6: R^1 = H, R^2= OCH_3, R^3= F
7: R^1 = OCH_3, R^2= H, R^3= H
8: R^1 = H, R^2= OCH_3, R^3= OCH_3

9a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= H
9b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= H
10a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= F
10b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= F
11a: X= Cbz, R^1 = OCH_3, R^2= H, R^3= H
11b: X= *p*Ts, R^1 = OCH_3, R^2= H, R^3= H
12a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= OCH_3
12b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= OCH_3

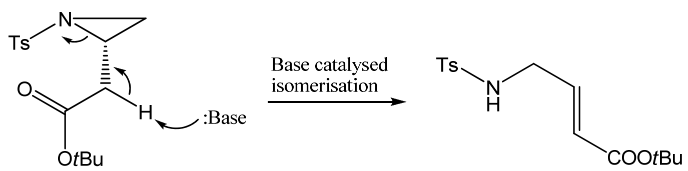
Scheme 2.12

Table 2.3: Nucleophilic ring-opening of aziridines by various aryl cuprates

Entry	Aziridine	ArBr	Product	Yield (%)	By-products[b]
1	**4a**	**5**	**9a**	60	$PhCH_2OH$
2	**4b**	**5**	**9b**	81	**13**
3	**4a**	**6**	**10a**	45	$PhCH_2OH$
4	**4b**	**6**	**10b**	49	**13**
5	**4a**	**7**	**11a**	51	$PhCH_2OH$
6	**4b**	**7**	**11b**	40[a]	**13**
7	**4a**	**8**	**12a**	6	$PhCH_2OH$
8	**4b**	**8**	**12b**	-	**13**

a) Isolated in a mixture with non-reacted aziridine **4b**.
b) Biaryls (Ar-Ar) were detected in all reactions.

The synthesis of various analogues required typically at least 2 equivalents of the respective Grignard-reagent to reach acceptable yields. Attempts with 1.0-1.5 equivalents of the nucleophile resulted in very low yields, and even failed to provide any product in some cases. In gram scale experiments, we found it necessary to add up to 3 equivalents of the aryl Grignard reagent due to significantly lower conversion. This was most probably due to factors like time and volume, resulting in a larger degree of decomposition of the Grignard-reagents. Compounds **9a** and **9b** were typically isolated in 60-80% yield, and represent the most successful ring-opening reactions. The fluorinated analogues **10a** and **10b** were more problematic, first of all due to lower conversion. Isolation of these two products **10a** and **10b** resulted typically in 45-50% yield. The *ortho*-analogues **11a** and **11b** were also challenging with respect to conversion, and were isolated in 40-50% yield. Reactions with the highly electron rich veratrole nucleophile, prepared from 4-bromoveratrole (**8**), proved to be very challenging. While a small amount of the product **12a** was isolated and characterised in 6% yield, no product **12b** was detected. In the ring-opening reactions of aziridine **4b** (entries 2, 4, 6 and 8), various amounts (4-27% yield) of *N*-Ts-alkene **13** were isolated as by-products, formed by base catalysed isomerisation (Scheme 2.13). Such base-promoted isomerisation reactions are well known from epoxides,[116] while for aziridines the literature is more limited.[117,118] However, a mechanism involving aziridinyl anions followed by a 1,2-H shift (chemistry recently reviewed by Florio and Luisi[119]) can not be excluded.



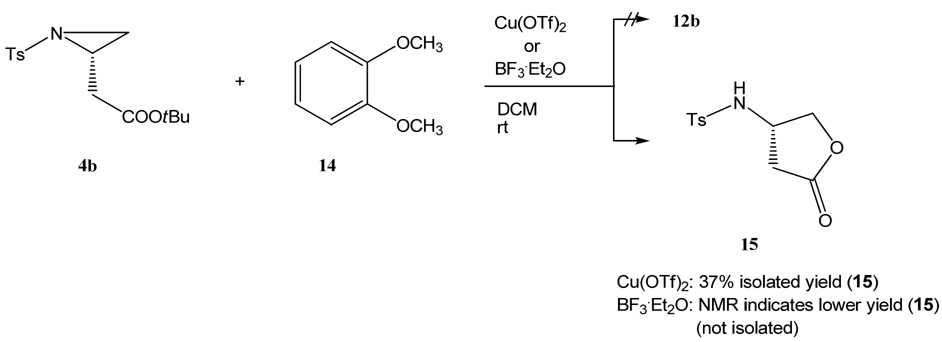
4b **13**

Scheme 2.13

Isolation of the ring opening products by flash chromatography turned out to be difficult in several cases, especially for the product **11b**, since unreacted aziridine **4b** tended to eluate very similarly. In the case of the product **10b**, a complete separation from alkene **13** was problematic. In all the ring-opening reactions with *N*-Cbz-aziridine **4a**, we observed various amounts of benzyl alcohol (up to 23% yield) in the crude reaction mixture. This is a typical by-product from the cleavage of Cbz-groups, and underscores that such protection groups are not compatible with hard organo-magnesium-reagents,[94d] unless very mild reaction conditions are provided. Other significant by-products were the respective biaryls (Ar-Ar), known as Wurtz coupling products, which appear especially with electron rich aryls.[120]

As a conclusion, our results revealed that the three copper anisole substrates, derived from arylbromides **5-7,** ring-opened aziridines **4a** and **4b** regioselectively. An obvious drawback was the conversion, providing typically moderate yields. Based on this, we are confident that with some more effort on optimisation, the yields might be improved. On the other hand, synthesis of the products **12a**/**12b** obviously requires completely different reaction conditions in order to succeed.

Motivated by that, we decided to investigate other possibilities to synthesise these veratrole derivatives. Turning our attention to Lewis acid catalysis, we decided to test the possible Friedel-Crafts type coupling between *N*-Ts-aziridine **4b** and veratrole **14**. An attempt with *N*-Cbz-aziridine **4a** was not even considered, because of the *N*-carboxyaziridines urge to rearrange to oxazolines under Lewis acid catalysis.[121]



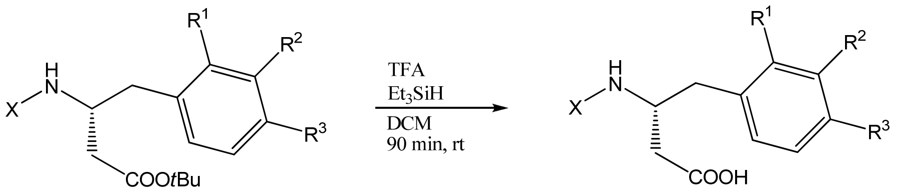
Scheme 2.14

Two classical azaphilic Lewis acids, Cu(II)triflate[122] and BF_3-etherate,[123] were tested and found to be unsuccessful for the envisioned reaction (Scheme 2.14). Both attempts provided lactone **15** as the main product, which was identified and characterised according to literature published by Bergmeier and co-workers.[124] Mechanistically, this is comparable to related *N*-Ts-aziridines (substituted with a β-ester function) which are reported to undergo base catalysed reactions to provide five membered lactone rings.[118] Successful ring-opening reactions by aryl systems are indeed found in the literature, but such *N*-Ts-aziridines are attached to α-phenyl moieties, capable of benzylic stabilisation of intermediate carbocations.[125,126] As a consequence, it appears that Lewis acid catalysed intermolecular ring opening reactions of *N*-Ts-aziridine **4b** with a β-carbonyl group, are suppressed by a rapid intramolecular cyclisation.

Alternative methods to synthesise veratrole derivatives **12a** and **12b** were not attempted, thereby deciding to surrender (*S*)-2-amino-6,7-dimethoxytetralin as a target molecule.

2.3.5 Deprotection of *tert*-butyl esters

A selective cleavage of the *tert*-butyl protective group in coupling products **9a**-**b**, **10a**-**b**, and **11a-b**, were required prior to cyclisation. This was performed according to the procedure published by Mehta and co-workers, in which acidolysis is performed with trifluoroacetic acid in DCM.[127] The improvement in this methodology compared with the classical approach can be subscribed to the addition of triethylsilane, which works as a carbocation scavenger. As a consequence, shorter reaction times and improved yields have been obtained. This method yields only volatile by-products and requires no aqueous work-up. Scheme 2.15 and Table 2.4 summarises the results obtained for the *tert*-butyl deprotection reactions.



9a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= H
9b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= H
10a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= F
10b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= F
11a: X= Cbz, R^1 = OCH_3, R^2= H, R^3= H
11b: X= *p*Ts, R^1 = OCH_3, R^2= H, R^3= H

16a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= H
16b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= H
17a: X= Cbz, R^1 = H, R^2= OCH_3, R^3= F
17b: X= *p*Ts, R^1 = H, R^2= OCH_3, R^3= F
18a: X= Cbz, R^1 = OCH_3, R^2= H, R^3= H
18b: X= *p*Ts, R^1 = OCH_3, R^2= H, R^3= H

Scheme 2.15

Table 2.4: Deprotection of *tert*-butyl esters by acidolysis

Entry	*t*-Bu ester	Acid	Yield (%)
1	**9a**	**16a**	78
2	**9b**	**16b**	89
3	**10a**	**17a**	12[a]
4	**10b**	**17b**	84
5	**11a**	**18a**	68
6	**11b**	**18b**	52[b]

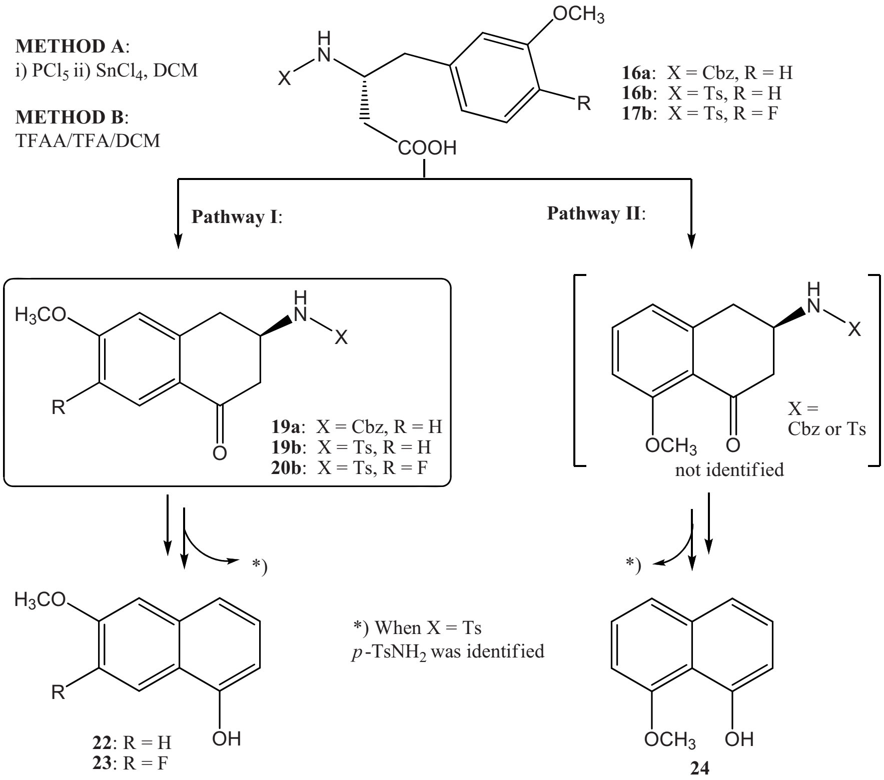
a) Unexpected problems during work-up. Decomposition of product.
b) Isolated as a mixture with N-Ts-lactone **15**.

After some initial testing, we decided to implement column chromatography as a final purification step to obtain pure acids, despite the fact that the expected by-products are volatile.[127] The ester cleavage gave moderate to good yields, with one exception. The crude reaction mixture of **17a**, indicated a high degree of conversion, but appeared as a rather complex crude mixture. Initial purification attempts by recrystallisation from diethyl ether/*n*-pentane failed. Later, by the aid of semi-gradient column chromatography, some pure material was isolated. However, the amount was not sufficient to attempt cyclisation of acid **17a**. Another observation was the transformation of *N*-Ts-aziridine **4b**, from the impure starting material of **11b**, to *N*-Ts-lactone **15**. This is basically the same reaction as described in Scheme 2.14, but in this case catalysed by a Brønsted acid instead of a Lewis acid.

2.3.6 Intramolecular cyclisation to tetralone frameworks

To construct the desired tetralone framework, acids **16a**-**b**, **17b** and **18a**-**b** had to be cyclised. To achieve that, we turned our attention to classical Friedel-Crafts (F-C) acylation reactions. Initially, a reagent for the preparation of the intermediate acid chloride was required. For this reaction, three well known reagents were considered, i.e. thionyl chloride ($SOCl_2$), oxalyl chloride ($(COCl)_2$) and phosphorous pentachloride (PCl_5). Initial test reactions were performed with substrates **16a** and **16b**, and it soon became evident that heating in thionyl chloride was not worthwhile, resulting in a gradually black coloured reaction mixture. Any attempts to isolate products or efforts to find an explanation for this destructive finding was not performed. Turning our attention to oxalyl chloride and PCl_5, we found that both were able to make the acid chlorides. In order to identify an optimal Lewis acid for the attempted cyclisation, several candidates were tested, i.e. aluminium(III)chloride ($AlCl_3$), tin(IV)chloride ($SnCl_4$), boron trifluoride etherate ($BF_3{\cdot}Et_2O$) and trimethylsilyl triflate (TMSOTf). After a series of initial approaches, we found that both, $AlCl_3$ and $SnCl_4$, were suitable for performing the cyclisation reaction. We decided to use the latter because of the practical volumetric addition. The PCl_5/$SnCl_4$-combination has also been used in several other reactions, with related substrates.[88,128-131] The reactions were typically run at 0 ºC or at room temperature.

As an alternative approach, the cyclisations were also performed using a protocol described by Gonnot and co-workers, utilising a mixed anhydride made from a TFAA/TFA-mixture in DCM.[132] At room temperature, an electron rich aryl intermediate was reported to provide a high yield within 15 min. An interesting observation is the fact that cyclisation occurs *meta* to the activating methoxy group, thereby suggesting that the activation is less crucial in this very reactive system. The results of our cyclisation attempts are described in Scheme 2.16, Table 2.5.



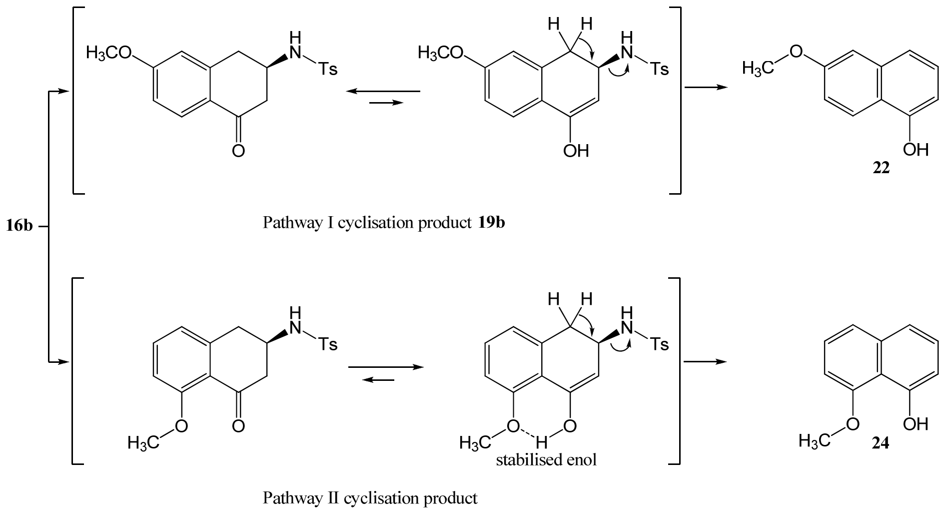
Scheme 2.16

Table 2.5: Cyclisation reactions of acid **16a-b** and **17b**

Entry	Acid	Meth.	Conditions	I : II[a]	Product	% Yield
1	**16a**	**A**	0 ºC (0.5 h) → rt (3 h)	97 : 3	**19a**	25
2	**16a**	**A**	0 ºC, 4 h	97 : 3	**19a**	28
3	**16b**	**A**	0 ºC (1 h) → rt (3 h)	95 : 5	**19b**	27[b]
4	**16b**	**A**	0 ºC, 6 h	91 : 9	**19b**	40
5	**16b**	**B**	rt, 0.5 h	78 : 22	**19b**	23
6	**16b**	**B**	rt, 16 h	78 : 22	**19b**	9
7	**17b**	**A**	0 ºC (1 h) → rt (3 h)	100 : 0	**20b**	39[c]
8	**17b**	**A**	0 ºC, 4 h	100 : 0	**20b**	41
9	**17b**	**B**	0 ºC, 4 h	100 : 0	**20b**	29

a) Indicates the ratio between Pathway I and II, estimated by ^{1}H NMR-analyses.
b) **22** (30% yield) and **24** (3% yield).
c) **23** (30% yield).

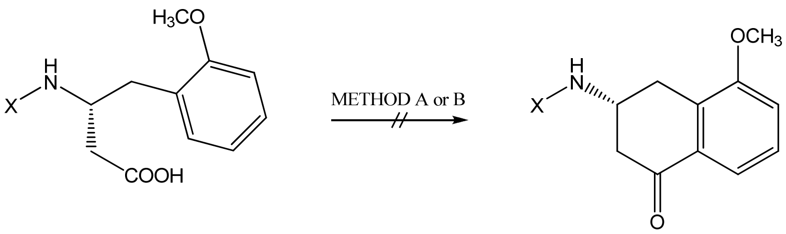
Focusing on the F-C acylation reactions of *N*-tosylated acids **16b** and **17b** (Method A), cyclisation of **16b** at room temperature (entry 3) resulted in significant amounts of naphthalenes **22** and **24**. Both of these compounds have been described in the literature.[133,134] From the same reaction mixture, *para*-toluenesulfonamide (*p*-$TsNH_2$) was also isolated. We rationalised these findings to result from an aromatisation of the products from the Pathway I and II cyclisations. Interestingly, we were not able to isolate the cyclisation product from Pathway II (Scheme 2.16). However, we observed that the total amount of the products **19b** and **22**, compared to the amount of product **24**, remained at a constant ratio during the reaction process. We therefore decided to use this as a value for the ratio between the respective reaction pathways. A possible explanation for these findings can be attributed the respective tetralone's keto-enol tautomerism. While product **19b** is most stable in the keto-form, as most ketones are, the Pathway II cyclisation product has a stabilised enol-form due to hydrogen bonding. This enol is the structure that causes a favourable aromatisation releasing naphthalenes (Scheme 2.17).



Scheme 2.17

Lowering the temperature from room temperature to 0 ºC improved the yield of **19b** from 27% to 40% (entries 3 and 4), but the regioselectivity was slightly lowered. The formation of the fluorinated analogue **20b** was entirely regioselective, and no Pathway II cyclisation product was observed. By-product **23** (Scheme 2.16) was isolated and characterised as a new monofluorinated naphthalene derivative. Running the reaction at 0 ºC instead of room temperature, improved the yield from 39% to 41% (entries 7 and 8). Comparison with the results of the alternative method B (entries 5, 6 and 8), show that the yields obtained were in the same range. Regarding the regioselectivity, it decreased in the case of **19b**, while **20b** still yields only the *para* products. Finally, we observed that *N*-Cbz acid **16a** reacted slightly more regioselectively than the *N*-Ts substituted analogue **16b**. The amount of by-products **22** and **24** were also significantly lower. However, the isolated yield was also in this case quite low (entries 1 and 2).

Cyclisation of **18a** and **18b** was in principle expected to occur *meta* to the methoxy group, producing only one product. However, attempts with both methods failed to give any sufficient amounts of product **21a** (Scheme 2.18).



18a: X = Cbz
18b: X = *p*Ts

21a: X = Cbz (trace amounts (**METHOD A**))
21b: X = *p*Ts (not identified)

METHOD A: i) PCl_5, ii) $SnCl_4$
METHOD B: TFAA/TFA

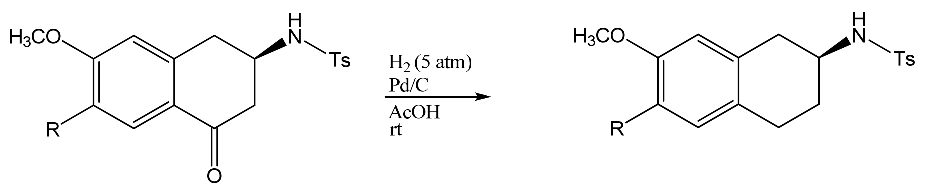
Scheme 2.18

As a conclusion, we did not reach higher than 41% yield in any of these attempts, which was rather discouraging. A main reason may be the somewhat surprising aromatisation reactions of **19b** and **20b**. In the case of *N*-Cbz acid **16a**, the amount of by-products indicate the occurrence of alternative reaction pathways.

In two recent publications, a combination of indium(III)bromide and dimethylchlorosilane was utilised as F-C acylation reagents.[135,136] Successful transformations were reported starting from the free acid, as well as various esters like *tert*-butyl-, benzyl- and isopropyl. The basis for these reactions was the observation that dimethylchlorosilane reacted with the acid (or ester) at the expense of it's silane proton, forming a chlorosilyl ester. This chlorosilylester was found to mimic an acid chloride in a F-C reaction, and through In(III)bromide catalysis, acylation reactions occurred. In a series of various reactions, both intra- and intermolecular, yields were reported to be good to mediocre. We decided to investigate this protocol and performed reactions with both acid **16b** and ester **9b**. However, both attempts failed to give tetralone **19b** at 80 ºC, according to the protocol. Decreasing the reaction temperature to 50 ºC resulted in a gradually decomposition of the starting material. Based on this, we decided to avoid this alternative "high" temperature approach, since the tetralone intermediates **16a**-**b** and **17b** had already proven to aromatise at relatively low temperatures (Scheme 2.16).

2.3.7 Deoxygenation of *N*-Ts tetralones

Deoxygenation of tetralones **19b** and **20b** were found to proceed well by medium pressure catalytic hydrogenation over Pd/C, in a modified literature procedure (Scheme 2.19).[89]



19b: R = H
20b: R = F

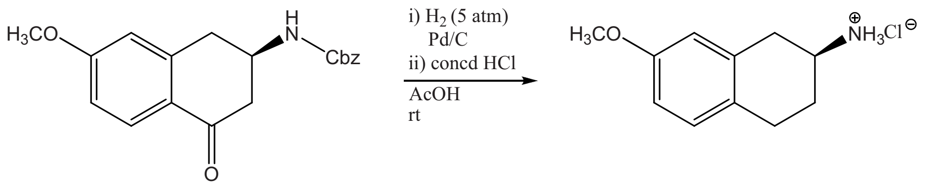
25b: R = H
26b: R = F

Scheme 2.19

Tetralins **25b** and **26b** were isolated in 57% and 76% yield, respectively. HPLC-analysis using a chiral column was performed for product **25b**, verified a high enantiopurity (99% ee).

2.3.8 One-pot deoxygenation and deprotection of *N*-Cbz-tetralone

Tetralone **19a** was deoxygenated and deprotected by a one-pot catalytic hydrogenation reaction over Pd/C (Scheme 2.20).



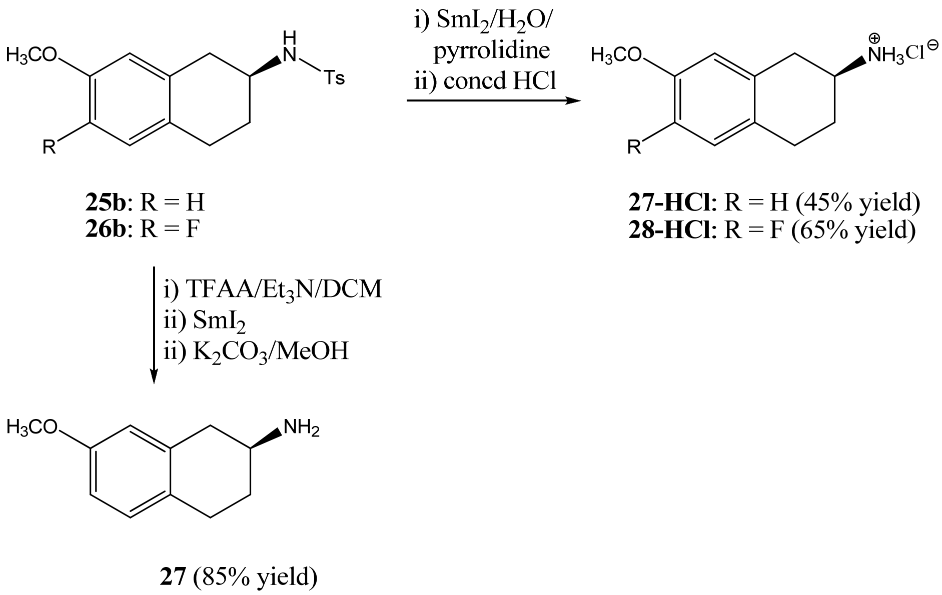
19a **27-HCl**

Scheme 2.20

The liberated (*S*)-2-amino-7-methoxytetralin (**27**) was transformed into an easy to handle HCl-salt **27-HCl** in 70% yield. Analysis showed consistency with the literature, without any significant signs of racemisation (99% ee).[91] (HPLC analysis on a chiral column performed after a derivatisation of **27-HCl** to tosylate **25b**.)

2.3.9 Deprotection of *N*-tosyl groups

Traditionally, rather harsh conditions are necessary to cleave tosyl groups from the amines. Typical one-electron transfer reagents like lithium or sodium have been utilised, which in many cases are not compatible with various functional groups. The same problem also arises when hydrolysis under very strong acid conditions (e.g. HBr, $HClO_4$) is attempted. More selective and sophisticated techniques utilising photoreactions, electrolysis or various metal reagents for the deprotection are known, but they tend to be non-general methods.[94e] In a very recent publication by Ankner and Hilmersson, an instantaneous and mild deprotection method was described.[137] In a combination of water and pyrrolidine (or other aliphatic amines), samarium diiodide is capable to cleave the protective group elegantly at room temperature. Scheme 2.21 describes our attempts to perform the deprotection according to this protocol.



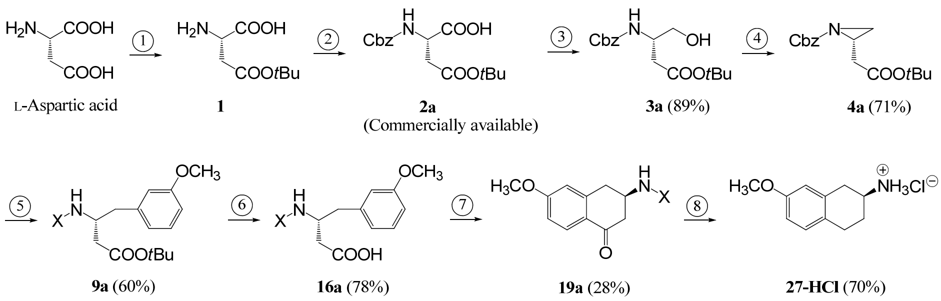
Scheme 2.21

Deprotection with SmI_2 proved to be both simple and extremely rapid. The isolated yields of **27-HCl** and **28-HCl** were 45% and 65%, respectively. The reason for these moderate yields can partly be attributed to the quality of the reagent, but also problems related to inaccuracy in small scale syntheses may not be excluded. Analysis of the optical purity also confirmed that no significant racemisation occurred.[26,91]

Another *N*-tosyl deprotection method is presented in chapter 4.3.7, where tetralone **27** was isolated in 82% yield from *N*-tosylamine **25b**. In this method, a trifluoroacetyl group adds to form a bis protected amine prior to the addition of SmI_2. After this detosylating step, basic hydrolysis cleaves the trifluoroacetyl-group and liberates the free amine **27** (see chapter 4.3.7 for details).

2.4 Summary

Aspartic acid 4-*tert*-butyl ester (**1**) was chosen as our starting material and three alternative *N*-protecting groups (Cbz, Ts and Boc) were evaluated. We were able to synthesise two out of four target molecules (**27-HCl** and **28-HCl**) by the developed methodology. Scheme 2.22 illustrates the synthesis of **27-HCl**, utilising Cbz as the *N*-protecting group, which provided the best result totally.



Scheme 2.22

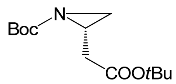
Reduction to the corresponding amino alcohols (**3a-c**) proved to be quite straightforward for carbamates **2a** and **2c**, but failed to reduce tosylate **2b** to *N*-Ts amino alcohol **3b**. To circumvent this, a transformation of **3a** to **3b** became the method of choice. Aziridinations of amino alcohols **3a**-**c** were synthesised utilising Mitsunobu conditions. Ring opening reactions with four bromoanisole derivatives worked satisfactory for three of them (2-bromoanisole, 3-bromoanisole and 5-bromo-2-fluoroanisole), while 4-bromoveratrole failed to produce any significant amounts of ring-opening products **12a** and **12b**. Hydrolyses of the *tert*-butyl esters resulted in good to moderate yields, with one exception (12% yield for **17a**). The most challenging step proved to be the cyclisations to the tetralone moiety. A typical Friedel-Crafts acylation and a mixed anhydride protocol were both tested, but we were not able to rise above 41% yield in any attempt. One of the main problems was the ability of the produced *N*-Ts tetralones (**19b**, **20b)** to aromatise into naphthalenes while eliminating $TsNH_2$. The stability of the Cbz protecting group also caused a problem in the synthesis of *N*-Cbz tetralone **19a**. Deoxygenation and deprotection of **19a** to target molecule **27-HCl** was a straightforward reaction, while **19b** and **20b** required a two step deoxygenation and deprotection procedure.

As a conclusion, we have developed a new total synthesis for substituted (*S*)-2-aminotetralins, where the key step is the fusion of the two synthons through a ring opening reaction of an aziridine with an appropriate nucleophile. With the exception of a problematic cyclisation step (41% yield and lower), the other steps provided decent yields. However, it was found that tosyl- and Cbz-protection of the amino group are not adequate for this total synthesis. If this synthesis should find a general application at a later stage, other protection groups must be evaluated. To broaden the amount of potential analogues, a larger effort in the optimisation of ring opening reactions of the aziridines has to be conducted, especially in the utilisation of very electron rich aromatic compounds (e.g. dimethoxybenzene). Limitations to very sterically demanding substrates might also be a factor to consider if one decides to attempt the synthesis of 2-aminotetralins with relatively large substituents.

2.5 Experimental

The full experimental description for Chapter 2 is reported in Paper I. Two exceptions which are not included in this paper are the experimental procedures and the data for compounds **4c** and **49,** which are provided below.

(*S*)-*tert*-Butyl 2-(2-tert-butoxy-2-oxoethyl)-aziridine-1-carboxylate (**4c).**

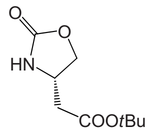


4c

Commercially available *N*-Boc-L-aspartic acid (**2c**) was reduced to the corresponding *N*-Boc-amino alcohol **3c** according to the procedure by Rodriguez and co-workers,[96] in 78% yield. The data for **3c** was compatible with the reported values from Hamprecht and co-workers.[138]

Alcohol **3c** (1.01 g, 3.66 mmol) and triphenylphospine (1.92 g, 2 equiv) were dissolved in dry THF (10 ml) and cooled to 0 °C. After addition of DEAD (1.14 ml, 2 equiv), the mixture was allowed to reach room temperature, and reacted further for 2h. The crude mixture was concentrated to approx 2 ml, before it was transferred to the chromatography column. Elution with 15% EtOAc in *n*-hexane provided 438 mg of **4c** (46% yield). Data for **4c**: R_f = 0.49 (15 % EtOAc in *n*-hexane). $[\alpha]^{rt}_{D}$ +70.5 (c 0.2, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 2.74-2.67 (m, 1H, CH-N), 2.62 (dd, *J*=15.8, 5.8 Hz, 1H, C**H**HC=O), 2,32 (d, *J*=6.0 Hz, 1H, C**H**H-N), 2.21 (dd, *J*=15.8, 7.0 Hz, 1H, CH**H**C=O), 1,99 (d, *J*=3.6 Hz, 1H, CH**H**-N), 1.47 (s, 9H, *t*Bu), 1.46 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz): δ 169.8 (RC(=O)O), 162.1 (OC(=O)N), 81.3 (*t*Bu), 81.1 (*t*Bu), 38.8 (**C**H_2C=O), 33.8 (CH-N), 31.3 (CH_2-N), 28.1 (*t*Bu), 28.0 (*t*Bu). IR (thin film, NaCl): 2979 (w), 1724 (m), 1394 (m), 1305 (m), 1257 (m), 1225 (m), 1154 (s), 854 (m) cm^{-1}. HRMS (ESI) calcd for $C_{13}H_{23}NO_4Na$ $(M+Na)^+$ 280.1519, found 280.1530.

(*S*)-*tert*-Butyl 2-(2-oxooxazolidin-4-yl)acetate (**49**).



49

Tosylation of *N*-Boc-alcohol **3c** was performed according to a literature procedure in 90% yield, and compatible data for tosylate **3c-Ts** were observed.[102] Tosylate **3c-Ts** served as the starting material in the synthesis of oxazolinone **49**, which was performed according to reaction conditions provided by a literature procedure.[139]

Tosylate **3c-Ts** (20 mg, 0,046 mmol) was dissolved in dioxane (1.0 ml) and added 2,4,6-trimethylpyridine (15 µl, 0.1 mmol) and $LiClO_4$ (49 mg, 0.46 mmol). The reaction mixture was heated to 70 ºC for 3 hours. At room temperature, the mixture was partitioned between EtOAc (10 ml) and 10% citric acid (10 ml). The aqueous layer was extracted with additional EtOAc (2 x 10 ml), and the combined organic fractions were dried ($MgSO_4$) and concentrated. Compound **49** was isolated as a colorless oil (7 mg, 74%). Data for **49**: R_f = 0.17 (40% EtOAc in *n*-hexane). ^{1}H NMR (400 MHz): δ 5.5 (bs, 1H, NH), 4.54 (dd, *J*=8.8, 8.3 Hz, CH**H**O), 4.23-4.11 (m, 1H, CH), 4.04 (dd, *J*=8.80, 6.00 Hz, 1H, C**H**HO), 2.59 (dd, *J*=16.8, 8.0 Hz, 1H, H-2), 2.52 (dd, *J*=16.8, 5.6 Hz, 1H, H-2), 1.46 (s, 9H, CH_3). ^{13}C NMR (100 MHz): δ 169.8 (C-1), 158.7 (NC(=O)O), 82.2 (**C**$(CH_3)_3$), 69.3 (CH_2O), 48.9 (CH), 40.7 (C-2), 28.1 (CH_3).

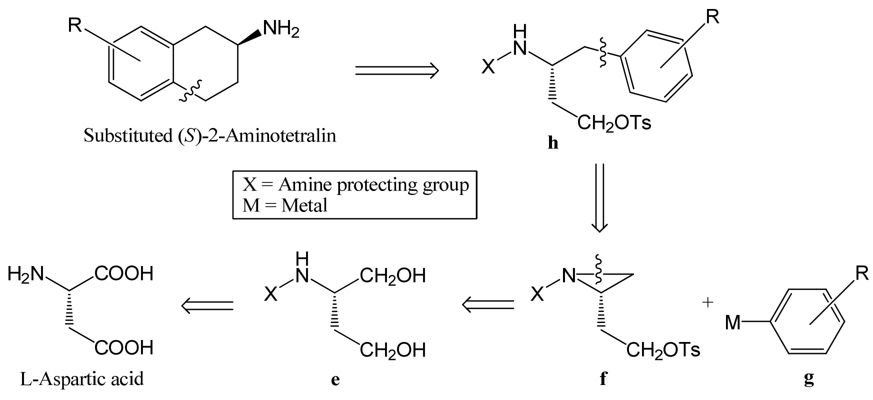
3 Chiral pool synthesis of 2-aminotetralins - Part II

3.1 Background

Based on the results described in Chapter 2, an alternative approach starting from L-aspartic acid was also evaluated. First of all, we decided to simplify the procedure by avoiding the selective β-esterification. Second, we wanted to make an aziridine precursor capable of performing the ring-closing reaction (aziridination) without the use of Mitsunobu-conditions (i.e. avoiding azo-reagents). And third, we had a strong urge to improve the troublesome tetralin cyclisation, and wished to test a different substrate with more suitable protection groups.

3.2 Retrosynthesis

In this attempt, L-aspartic acid is *N*-protected and reduced to a diol (**e**). The aziridine **f** can then be obtained through a double tosylation of the free OH-groups of the diol **e**. Regioselective ring opening of the aziridine **f** by an aryl nucleophile (**g**) should then provide the ring-opened product (**h**). Final cyclisation may then be performed to the desired 2-aminotetralin. (Scheme 3.1):



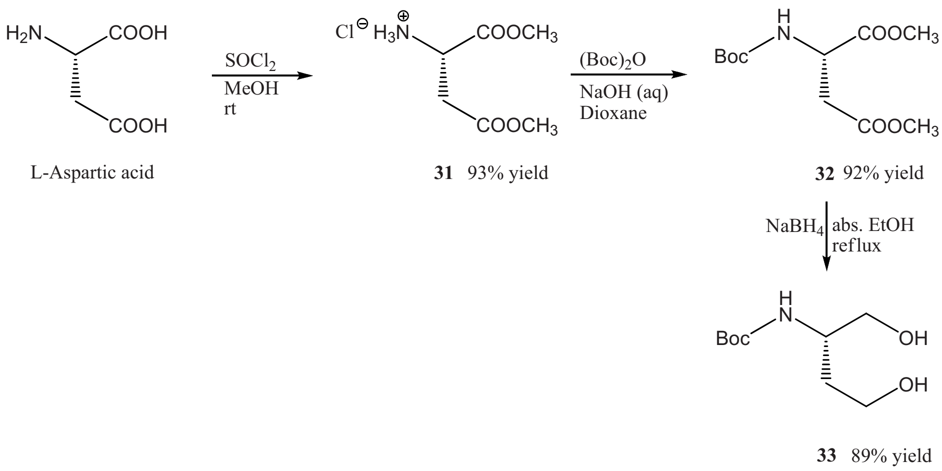
Scheme 3.1

3.3 Results and discussion

The total synthesis presented here in chapter 3 aims to be a general route towards enantiopure 2-aminotetralins, with various aryl substituents. In the development and evaluation of the stepwise process, however, only (*S*)-2-amino-7-methoxytetralin (**27**) was chosen as target molecule.

3.3.1 Preparation of *N*-Boc protected diol

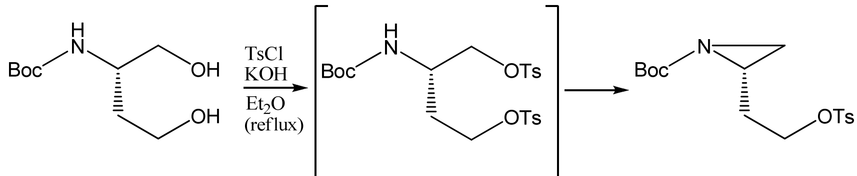
Aspartic acid was esterified in methanol in the presence of thionyl chloride, by the procedure of Gmeiner and co-workers (Scheme 3.2).[140] A simple work-up was sufficient to yield the relatively pure amino acid ester **31** as a hydrochloride salt. Subsequent protection of the amine function was performed by the introduction of a Boc-group, yielding *N*-Boc-ester **32** in 92% yield. The procedure was based on a patent description, for the protection of an analogue diethyl ester.[141] After a work-up with careful pH-control, pure crystalline product **32** was isolated. Reduction was performed with $NaBH_4$ in refluxing ethanol.[141] After a rather tedious work-up, including several extractions, diol **33** was isolated in 89% yield (Scheme 3.2).



Scheme 3.2

3.3.2 Ring-closing reaction to aziridine

Keeping our experiences from chapter 2.3.3 in mind, we did not believe that tosylation and aziridination of *N*-Boc-diol **33** was the right approach because of the expected oxazolinone formation. However after discovering a successful cyclisation reaction presented by Wessig and Schwartz,[142] we decided to pursue this strategy. In this protocol, excess *p*TsCl and powdered KOH react in boiling diethyl ether with *N*-Boc-β-amino alcohols, forming the respective aziridines. After some testing we were able to synthesise *N*-Boc-aziridine **34** in 76% yield (Scheme 3.3).

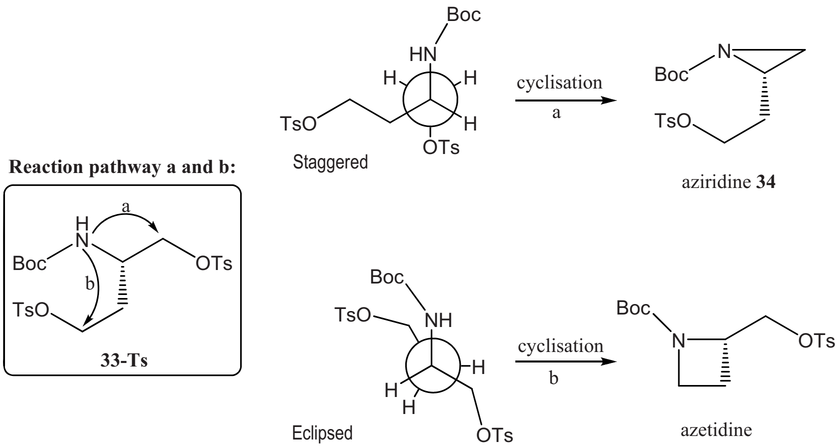


33 **33-Ts** **34** 76% yield

Scheme 3.3

Based on our previous experiences, and now from the successful aziridination of **33** (and more supporting literature[143-146]), it appears that strong basic (i.a. KOH, NaH, LiHMDS, Et_3N) conditions for tosylated (or mesylated) *N*-acyl (or *N*-carbamoyl)-β-amino alcohols may have two distinct outcomes, i.e. aziridination or oxazolinone formation. However, we were not able to predict the preferred outcome for these reactions, concluding that the reactions are strongly substrate dependent.

This result also demonstrates quite clearly that substrate **33** has a strong preference to undergo cyclisation to our target molecule, a three membered aziridine ring (**34**), rather than a potential four membered azetidine ring (Scheme 3.4). This can be explained by the conformations of **33-Ts** responsible for the respective cyclisations, where **34** is formed through the more favourable staggered conformation. In terms of entropy factor, attack on the β-position is strongly favoured, with a reaction rate about 100 times higher than a γ-position attack.[147] Nevertheless, in a related example with a very sterically demanding *N*-protective group (Pf), a preference for azetidine formation on the expense of aziridine formation, has been demonstrated.[139]

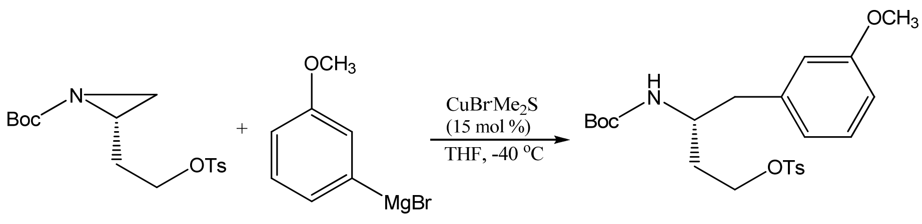


Scheme 3.4

In conclusion, this method seems to work surprisingly well and reaction mixtures do not indicate any significant by-product besides various amounts of unreacted **33-Ts**. Another positive consequence of this method was the remaining tosyl group, which could serve as a protection group in the next step (see chapter 3.3.3).

3.3.3 Ring-opening reaction by aryl nucleophiles

By using the same methodology as described in chapter 2.3.4, we were able to successfully ring-open aziridine **34** with the aryl nucleophile made from 3-bromoanisole (**5**) (Scheme 3.5). The reaction required at least 2 equivalents of the Grignard-reagent to achieve high conversion and yield.



34 **5-Mg** **35** (80% yield)

Scheme 3.5

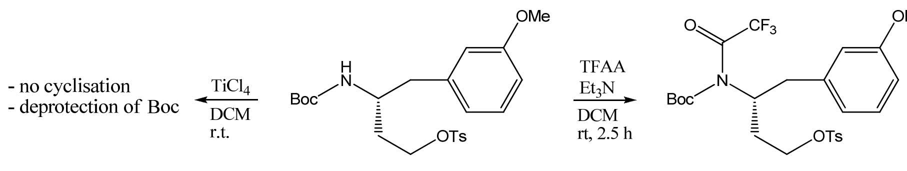
It soon became evident that the compound was somewhat unstable. Stability tests performed revealed that 50% of the product had decomposed after 6 hours in boiling THF, and 23% decomposed in boiling DCM within the same time. As a consequence, drying of the purified product **35** was performed at room temperature (high vacuum) before storage at low temperature (-18 ºC).

To synthesise target molecule (*S*)-7-methoxy-2-aminotetralin (**27**) from tosylate **35**, two alternative approaches were tested. The results of the intramolecular Friedel-Crafts alkylations are summarised in the following chapter, while the results from the cyclodehydration strategy are presented in chapter 3.3.5.

3.3.4 Intramolecular Friedel-Crafts alkylation

A standard procedure for a Friedel-Crafts (F-C) reaction typically utilises an acyl- or alkyl halide, with an appropriate Lewis acid. Generally, F-C acylations work better than the alkylations, which require tougher reaction conditions and may give additional alkylations due to increased ring activation.[148] Little is known about the possibilities for intramolecular F–C alkylations of alkyl tosylates, or other sulfone based (e.g. mesyl, triflate) leaving groups.

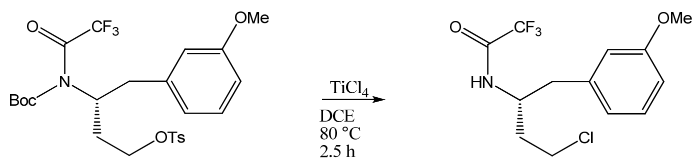
To pursue this possibility, an initial test reaction with tosylate **35** was performed under F-C conditions (Scheme 3.6). Early observations revealed, however, that cleavage of the Boc-group occurred rapidly even at room temperature. To circumvent this problem, a replacement of the Boc-group by a more Lewis acid stable protecting group seemed to be essential. To achieve this, a trifluoroacetyl group was introduced to double protect the amine function. This choice was based on the results presented in Scheme 2.2, demonstrating the Lewis acid compatibility of trifluoroacetylamines. Another factor was the simple introduction and deprotection protocols for this group.[94g] Scheme 3.6 demonstrates the introduction of the trifluoroacetyl group to the double protected amine **36**.



35 36 (99% yield)

Scheme 3.6

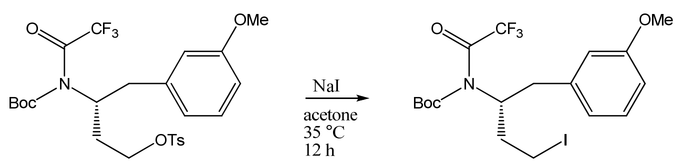
Attempts to perform a intramolecular F-C type cyclisation of tosylate **36** was, however, unsuccessful with titanium(IV) chloride (80 °C, DCE). Analysis of the main product revealed that not only was the Boc group cleaved off, the tosyl group was exchanged by a chloride as well (see Scheme 3.7).



36 37 (58% isolated yield)

Scheme 3.7

A similar observation from the literature supports this substitution, when a oxophilic Lewis acid like titanium(IV) chloride was used in a reaction with an alkyl tosylate.[149] Through the newly formed alkyl chloride **37**, we now had synthesised a substrate suitable for classical F-C alkylation reaction.

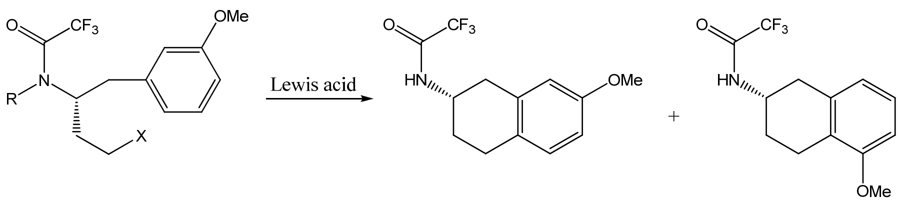


36 38 (78% yield)

Scheme 3.8

For comparison to the chloride **37**, we also decided to synthesise the corresponding iodide from tosylate **36**. The main reason for this was to broaden the possibilities of combining both hard and soft alkyl halides with various Lewis acids. Iodide **38** was prepared through a typical substitution reaction protocol with sodium iodide in acetone (35 °C), in 78% yield (Scheme 3.8).[150]

The results from the cyclisation reactions of chloride **37** and iodide **38** are summarised in Scheme 3.9 and Table 3.1:



37 (X = Cl, R = H)
38 (X = I, R = Boc)

39

40

Scheme 3.9

Table 3.1: Cyclisation of chloride **37** and iodide **38** under various reaction conditions

Entry	Substrate	Solvent	Lewis acid	Temp (ºC)	Time (h)	Ratio[b] **39** : **40**	**39** % yield[c] (% ee)[d]
1	**37**	DCE	$AlCl_3$ (2 equiv)	80	7	-	-[e]
2	**37**	DCE	$AlCl_3$ (2 equiv)	reflux	20	-	-[e]
3	**37**	DCE	$InBr_3$ (2 equiv)	reflux	20	69 : 31	complex mixture
4	**37**	DCM	$AlCl_3$ (3 equiv)	100[a]	20	83 : 17	36% (99% ee)
5	**37**	DCM	$InBr_3$ (2 equiv)	80[a]	20	68 : 32	<15% (99% ee)
6	**37**	DCM	$SnCl_4$ (3 equiv)	80[a]	20	-	-[e]
7	**37**	DCM	$BF_3 \cdot Et_2O$ (3 equiv)	80[a]	20	-	-[e]
8	**38**	DCM	$InBr_3$ (2 equiv)	80[a]	18	71 : 29	26% (97% ee)

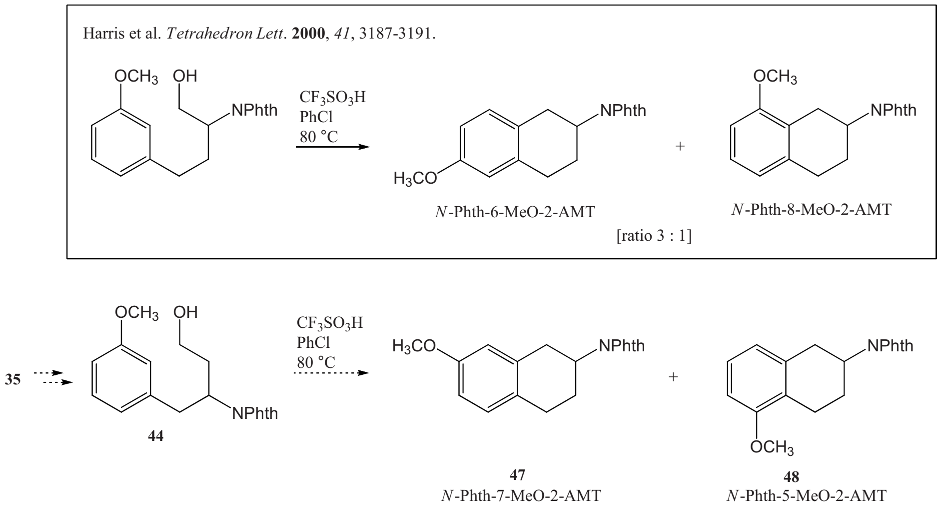
a) Reaction performed in closed pressure tube.
b) Ratio determined according to ^1H NMR spectrum of the product mixture.
c) Isolated yield after purification.
d) The enantiomeric excess of the products was determined by HPLC.
e) No reaction.

The results from the reactions in Table 3.1 demonstrate that both, chloride **37** and iodide **38**, can be cyclised into our target molecule **39**, but the reactions were not entirely regioselective, i.e. significant amounts of *ortho* product **40** was formed as well. A comparison of entry 4 with entries 3, 5 and 8, indicates that aluminium(III) chloride gives a significantly better regioselectivity than indium(III) bromide, even at a higher reaction temperature. Isolated yields are moderate to low in these initial attempts, but if some optimisation effort can be performed, more decent yields should be within reach. Products **39** and **40** were only partly separable by column chromatography, so improved chromatographic conditions are also required. Analyses of the enantiomeric excess revealed that the racemisation does not represent any problem in the total syntheses from enantiopure L-Aspartic acid.

Our target molecule (*S*)-7-methoxy-2-aminotetralin (**27**) is accessible through basic hydrolysis of trifluoroacetyl amine **39**, following a procedure (K_2CO_3, $MeOH/H_2O$, rt) described by Gómez-Sánches and co-workers, in up to quantitative yields.[151]

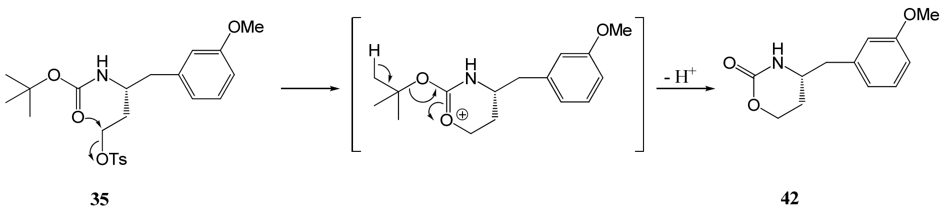
3.3.5 Phthalimide protection and cyclodehydration reaction

An alternative to the intramolecular Friedel-Crafts alkylation strategy is the cyclodehydration of the corresponding alcohol. Since the mid thirties, acid catalysed cyclodehydration of 4-phenylbutanols to their corresponding tetralins have been known.[152,153] More recently, methods utilising stoichiometric amounts of triflic acid or phosphoric acid have successfully been implemented in cyclodehydrations of electron rich arenes.[154,155] Inspired by the work published by Harris and co-workers,[154] we decided to investigate if tosylate **35**, after a transformation to the acid stable phthalimide **44**,[94h] would cyclise correspondingly (Scheme 3.10). Based on this, we aimed to synthesise the phthalimide protected target molecule **44**, which is a structural isomer of the one published by Harris and co-workers.



Scheme 3.10

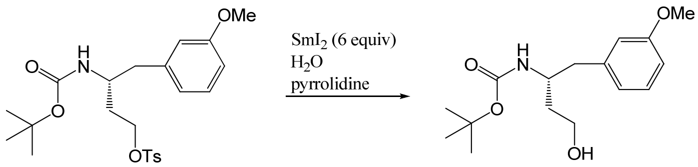
Since compound **35** is prone to react rapidly with nucleophiles in tosylate substitution reactions, we found it necessary to replace tosyl by a hydroxyl group. Early test reactions with excess KOH indicated that the cleavage was quite efficient, but it was accompanied by the loss of the Boc protection group. Analyses revealed that under these conditions, carbamate **42** was formed. A plausible mechanism for this elimination and cyclisation process is shown in Scheme 3.11.



Scheme 3.11

Two sets of reaction conditions were found to execute the synthesis of cyclic carbamate **42** efficiently, i.e. in DMSO at room temperature and in aqueous dioxane at 50 ºC. The prior conditions provided a yield up to 60%.

An alternative for the tosyl-cleavage with hydroxide nucleophiles is the application of samarium(II)iodide in a one electron transfer mechanism.[137] This method is applicable to both *O*-Ts and *N*-Ts groups, as already demonstrated in section 2.3.9. Based on this, we tested the conditions for compound **35** (Scheme 3.12).

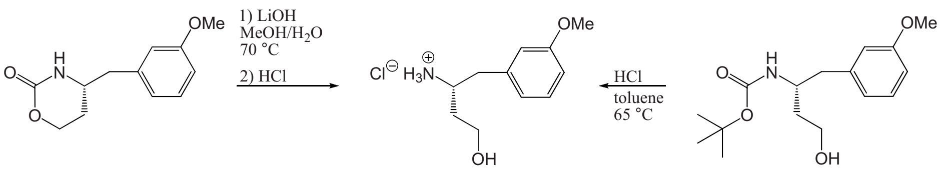


35 **41**

Scheme 3.12

It early became evident that this reaction system was not very efficient. Even with six equivalents of SmI_2, the turnover was still moderate and provided several products. One possible explanation is the lack of stability of the reagent. While the SmI_2-reagent was freshly prepared (samarium, diiodoethane, THF, rt, 1h) before the reaction in the above mentioned literature, only premade solutions from a chemical supplier were tested in our case. In a specific test with a newly opened bottle of SmI_2 in THF, we were only able to isolate **41** in 32% yield. Based on this, and the fact that this reagent is relatively expensive, this pathway was discarded.

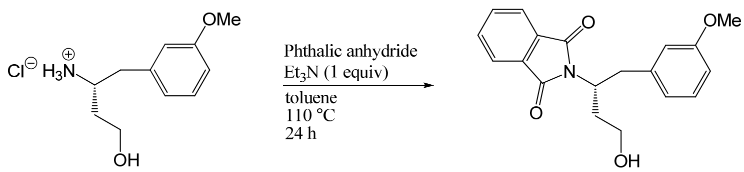
Through different *N*-Boc deprotection reactions of compounds **41** (HCl, toluene, 65 °C) and **42** (LiOH, MeOH/H_2O, 70 °C then HCl-treatment), we were now able to synthesise amine **43** as an HCl-salt (Scheme 3.13).



42 **43** **41**

Scheme 3.13

The cyclic carbamate **42** was opened by lithium hydroxide hydrolysis, using a modified procedure published by Curtis and co-workers in 65% yield.[156] Liberation of the *N*-Boc protection group in carbamate **41** was performed by treatment with hydrochloric acid in toluene at 65 °C, giving 80% yield.[157] Through these two alternative pathways, amine **43** was now accessible for protection to the double *N*-protected and acid stable phthalimide compound **44** (Scheme 3.14).

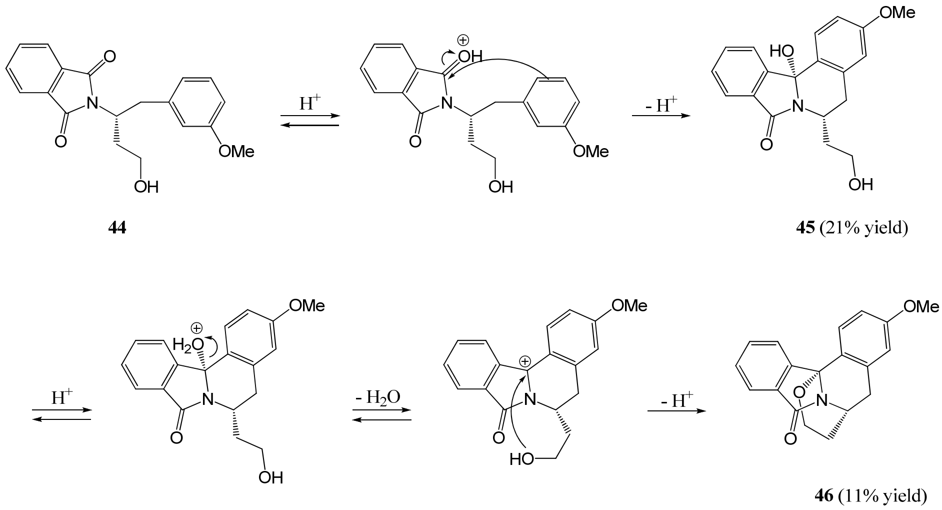


43 **44** 43% isolated yield

Scheme 3.14

The reaction was performed with freshly prepared phthalic anhydride (double recrystallised from $CHCl_3$ and dried) and dry toluene.[158] Despite of that, we only achieved 43% yield of **44** after several attempts. A probable reason for the moderate yield can be ascribed to the fact that we did not utilise a Dean-Stark apparatus, which would efficiently remove the produced water and thereby shift the reaction towards the product **44**. For larger scale reactions (here approx 100 mg **43**) and with the above mentioned equipment, we expect this reaction to proceed in potentially higher yields.

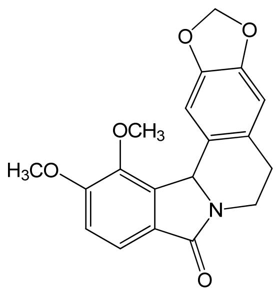
The target molecule **44** was tested under the reaction conditions (F_3CSO_3H, PhCl, 80 °C, 4h) for cyclodehydration, as described by Harris and co-workers[154] (Scheme 3.8). The reaction provided several products, but the two main products **45** and **46** were isolated and investigated closer. After initial ^1H and ^{13}C NMR analyses, we observed that for both products, the phthalimide ring system was not intact. Both structures gave rise to six non-equivalent aromatic carbon atoms and only one carbonyl signal. Through these observations, a reaction involving the phthalimide group was suggested. After more thorough analyses, we now believe that Scheme 3.15 describes the outcome of this reaction.



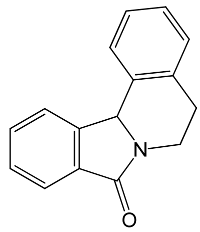
Scheme 3.15

Compound **45** (absolute configuration determined by NOESY experiments) results from the initial reaction with the phthalimide group. Product **46** is the result of an additional dehydration step with the intramolecular formation of an ether linkage, forming a favourable six membered ring.

Compounds **45** and **46** can be classified as isoindolo[1,2-a]isoquinolinone derivatives, related to the natural product (±)-nuevamine (Figure 3.2), isolated from *Berberis darwinii* Hook species.[159] This isoquinoline alkaloid is still considered as the only representative of this family, nevertheless, several general approaches to synthesise isoindolo[1,2-a]isoquinolinones (general structure, see Figure 3.1) have emerged in literature.[160-163] This might be due to the fact that several derivatives are considered to have potential biological activities.[164]



(±)-Nuevamine



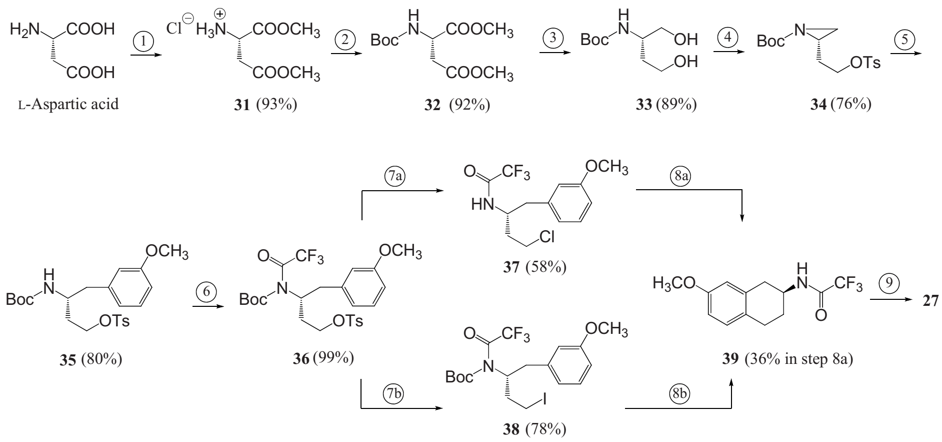
Isoindolo[1,2-a]isoquinolinone

Figure 3.1: Structures of (±)-nuevamine and isoindolo[1,2-a]isoquinolinone

Further work with compounds **45** and **46** were not pursued at this stage.

3.4 Summary

Chapter 3 describes the results of a new nine step total synthesis of (*S*)-7-methoxy-2-aminotetralin (**27**) from natural L-aspartic acid (Scheme 3.16). Several improvements have been achieved in this synthetic route compared with the one described in Chapter 2. The first obvious improvement is the fact that we were able to circumvent the selective β-carboxylic acid protection of L-aspartic acid. Second, no diazo-reagent (DEAD) was required in the ring-closing reaction to the aziridine **34**. And third, introduction of a trifluoroacetyl amino protecting group in Step 6 resulted in a robust and stable substrate able to sustain though Friedel-Crafts conditions. All steps provided the products in good to excellent yield with the exception of the intramolecular F-C alkylation reactions. Hence, to significantly improve this new route, further efforts in the optimisation of this step have to be conducted. With respect to enantiomeric excess, no racemisation was observed, yielding **39** in high enantiomeric purity (97 and 99% ee).



Scheme 3.16

In the alternative strategy based on cyclodehydration of the phthalimide protected alcohol **44** (Chapter 3.3.5), we were not able to synthesise our target molecule **27**. Instead we isolated compounds **45** and **46** that are related molecules to the isoindolo[1,2-a]isoquinolinone family. No further work, apart from the characterisation of these compounds, was performed.

3.5 Experimental

The full experimental description for Chapter 3 is reported in Paper II.

4 Asymmetric catalytic aziridination

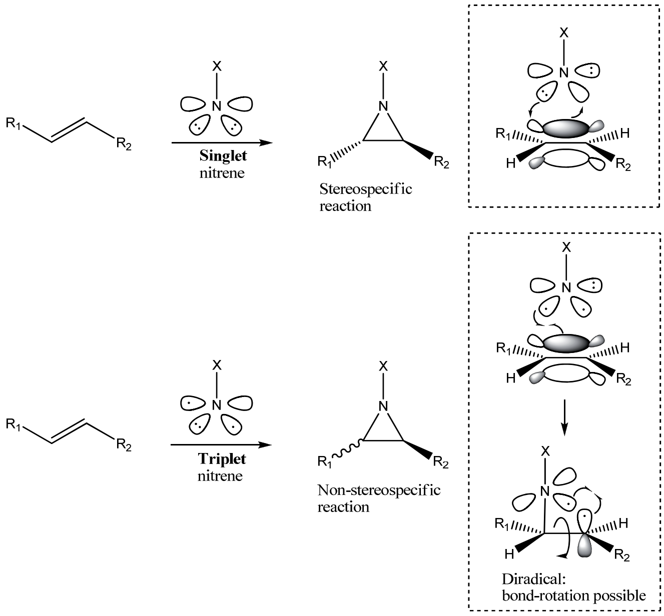
4.1 Background

Aziridination by nitrene addition to alkenes has been known for quite some years.[165,166] Early publications reported that this synthetic approach requires harsh reaction conditions, resulting in a total lack of stereoselectivity.[167] Since the mid nineties however, metal stabilised nitrenes have emerged as useful chiral catalysts in asymmetric aziridinations.[168] This has greatly extended the methodologies for synthesising enantiopure aziridines.

In the following parts of chapter 4.1, a brief introduction to nitrenes and an overview of the most commonly used metal-catalysts will be presented. The intention of this is to highlight the current knowledge about catalytic systems used in asymmetric aziridinations of alkenes.

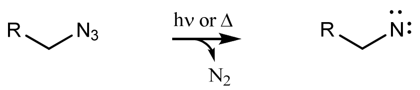
4.1.1 Nitrenes and nitrene precursors

Nitrenes are reactive intermediates where nitrogen bears only one substituent, plus additional four non-bonded electrons.[169] Depending on these non-bonded electrons, they can be classified as *singlet* or *triplet* nitrenes. In the former and most reactive state, they are arranged in two anti-parallel electron pairs. While in the latter and less reactive state, one orbital is filled with an anti parallel electron pair and two other orbitals have single electrons with a parallel spin. In aziridination reactions of unsymmetrical alkenes, singlet and triplet nitrenes react differently. While singlet nitrenes reacts in a concerted process, the triplet state reacts in a two step process, with the possibility of free bond rotation in the intermediate diradical. As a consequence, singlet nitrene reactions are stereospecific, while triplet nitrene react non-stereospecifically (Scheme 4.1).[51]



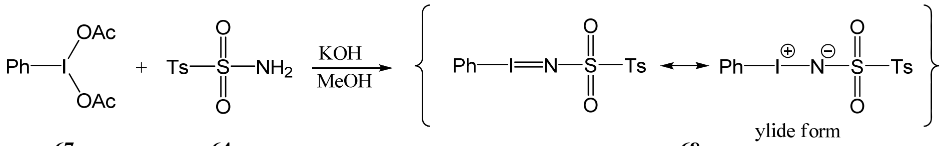
Scheme 4.1

Traditionally, nitrenes have been generated under relatively harsh conditions by thermal or photochemical decomposition of azides (Scheme 4.2).



Scheme 4.2

In 1975, the synthesis of *N*-tosyliminoaryliodinane **68** from iodobenzene diacetate **67** (hypervalent iodine compound) and *p*-tosylamide **64**, was presented as a new type of *I*-*N* ylide (Scheme 4.3).[170] The decomposition product of this ylide was found to possess an electrophilic character, which reacts with nucleophiles like thioanisole and triphenylphosphine. Such reactions are proposed to proceed via a sulfonyl nitrene intermediate, thereby defining **68** as a nitrene precursor.



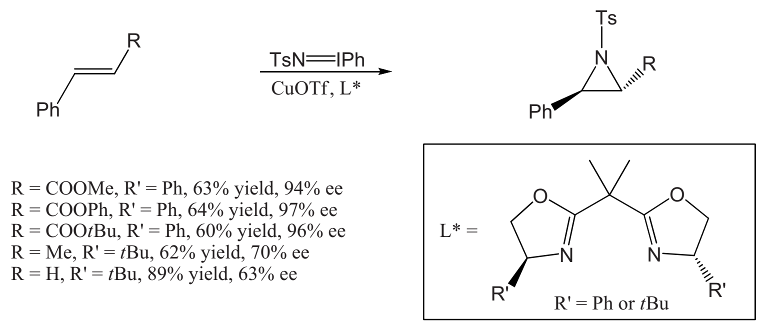
67 **64** **68**

Scheme 4.3

These types of compounds have later been found very useful as nitrogen sources in asymmetric aziridinations of alkenes, which will be discussed in the following chapters.

4.1.2 Evans and Jacobsen's copper catalysed aziridinations

Precursor **68** was the reagent of choice in the copper catalysed aziridination of alkenes, published by the group of Evans.[171] In their development of this synthetically useful method, Cu(I) and Cu(II) salts in acetonitrile were found to be the best catalyst/solvent system. The yields obtained, of the various aziridines, were quite substrate dependent and varied from low to excellent (23-95%). However, to achieve enantioselective nitrene transfer, chiral ligands of the bis(oxazoline) type (see general structure of L*, in Scheme 3.4) were later successfully implemented.[172] Scheme 4.4 demonstrates a series of representative examples utilising this methodology.



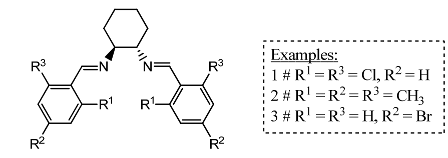
Scheme 4.4

Alternative aryl substituents have also been an object of investigation. Aryl rings bearing electron withdrawing (*p*-nitro, *o*-nitro, *p*-trifluoromethyl), electron donating (*p*-

methoxy) and sterically demanding (*p-tert*-butyl) groups have all been synthesised and tested as alternatives to compound **68**.[173]

The development of bis(oxazoline) ligands by the Evans group has contributed to the development of a range of other bis(oxazoline)-metal complexes, within a broad range of applications, which have been summarised in several review articles in recent time.[174,175]

Parallel to the work done by the group of Evans, Jacobsen and co-workers published catalytic systems utilising chiral diimine ligands together with nitrene precursor **68** and different Cu(I) salts.[176,177] After unsuccessful attempts with tetradentate (salen)Cu(II) complexes, they realised that bidentate chelation to copper was a requirement. This resulted in a series of benzylidene derivatives of 1,2-diaminocyclohexane, capable of performing stereospecific aziridinations (Figure 4.1).



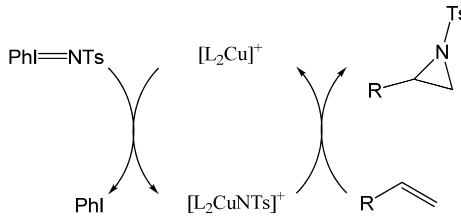
Jacobsen's dibenzylidene diimines

Figure 4.1

In a comparison of these two dominant catalytic systems, the Evans bisoxazoline ligands are considered as more successful for *trans*-alkenes, whereas the Jacobsen's diimines are better suited for *cis*-alkenes.[178] Both Cu(I) and Cu(II) metal sources form catalysts with the respective ligands, indicating a common oxidation state. Beside this, both catalytic systems seem to perform within a quite limited substrate range.

With respect to the mechanism of copper catalysed aziridination with PhI=NTs as nitrene source, Jacobsen was the first to suggest a mechanism.[177] This mechanism was later supported by a mechanistic study by Brandt and co-workers.[178] Scheme 4.5

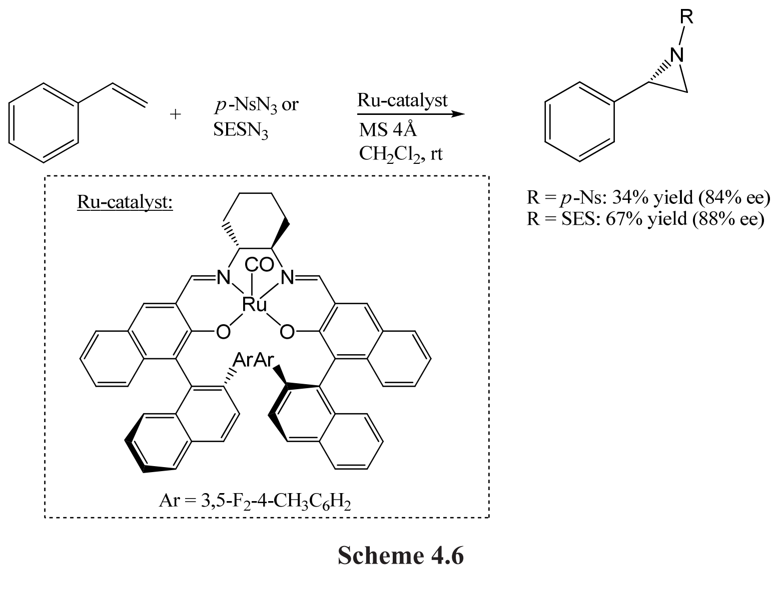
demonstrates this general mechanism, where L_2 symbolises the respective bidentate ligands in Evans and Jacobsen's catalytic systems.



Scheme 4.5

4.1.3 Ruthenium catalysts

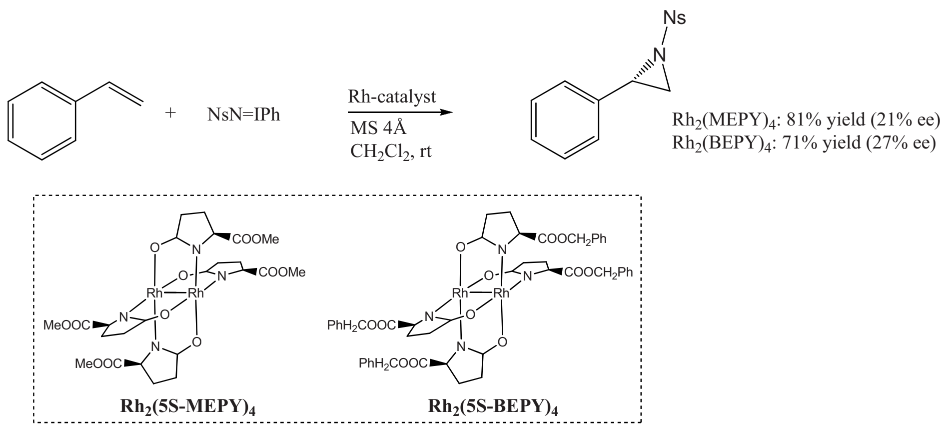
More recently, advances in ruthenium catalysis by Katsuki and co-workers have been reported.[179,180] Robust Ru(salen)CO complexes have been found useful in asymmetric aziridinations, for both *ortho*- and *para*-Ns azides as well as for SES (2-(Trimethylsilyl)ethane sulfonyl) azide. The promising results from the latter azide also include the advantage of an easy removable *N*-protecting group. The examples below (Scheme 4.6) highlight two of these results from aziridinations of styrene.



Scheme 4.6

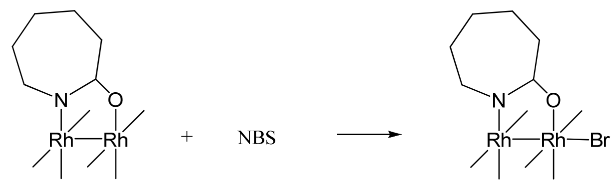
4.1.4 Rhodium catalysts

Rhodium(II) catalysts have been reported to be quite successful in asymmetric carbene transfer reactions, analogue to Cu(I) catalysts.[168] Their use in nitrene transfer reactions was early investigated, but they were found to be less efficient than the copper catalytic systems. However, some chiral Rh-complexes have been reported to give aziridines in quite high yields, but unfortunately with low or even no enantioselectivity.[181,182] Two of these catalysts are presented below (Scheme 4.7), in the aziridination reactions of styrene, utilising NsN=IPh as a nitrene precursor.



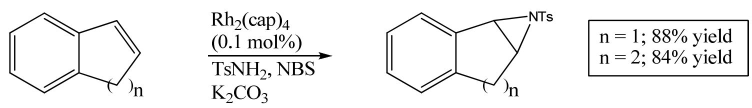
Scheme 4.7

In a recent publication from Doyle's group, a mixed-valent dirhodium(II, III) caprolactamate is used as a catalyst in aziridinations of alkenes.[183] This catalyst is formed by reacting dirhodium(II) caprolactamate [$Rh_2(cap)_4$] **77** with NBS (*N*-bromosuccinimide) in a one-electron oxidation, yielding the paramagnetic mixed-valent complex **78**. Scheme 4.8 demonstrates this redox process, with simplified rhodium complex structures (only one of the four caprolactam units is drawn).



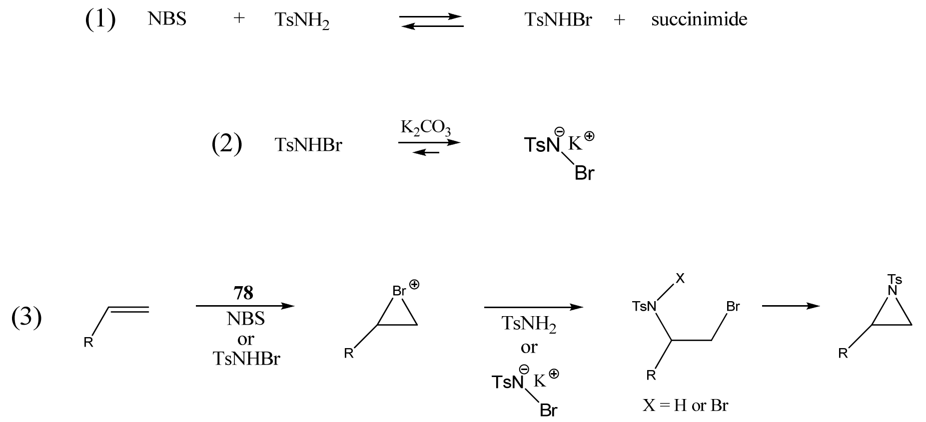
Scheme 4.8

The basis for this catalyst's effectiveness is the ability to undergo facile atom-transfer redox chemistry (Rh_2^{4+}/Rh_2^{5+}) because of its low one-electron oxidation potential.[184] In a combination with NBS, *p*-toluenesulfonamide and potassium carbonate, a range of aziridines were synthesised by the group of Doyle. Scheme 4.9 exemplifies two of the specific aziridination reactions.



Scheme 4.9

A closer study of the catalysts role has also revealed that no nitrene intermediate is present in reactions of this kind. On the other hand, an ionic mechanism is found to be operative. Mechanistically, catalyst **78** operates as a Lewis acid and is capable of generating other potentially useful intermediates. If we consider the proposed mechanism in Scheme 4.10, we first observe that NBS and $TsNH_2$ are found to be in an equilibrium with TsNHBr and succinimide (1). By the addition of a base (K_2CO_3), the equilibrium is shifted towards the deprotonated salt of potassium bromotosylamide (2).

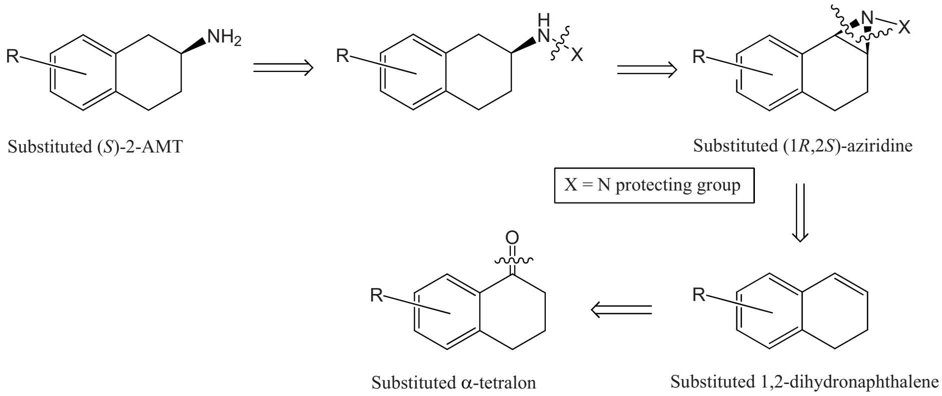


Scheme 4.10

The mixed-valent rhodium complex (**78**) is thought to function as a Lewis acid to activate residual amounts of NBS and/or TsNHBr, catalysing electrophilic bromonium ion transfer to an alkene. Capture of $TsNH_2$ (or KNTsBr) makes up the structural motif, which is able to spontaneous ring-close to the aziridine (3). Whether or not the mixed-valent complex **78** plays another vital role in the reaction, beyond as Lewis acid catalyst, remains uncertain.

4.2 Retrosynthesis

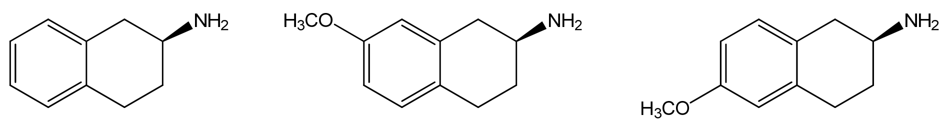
The strategy of catalytic asymmetric aziridination is based on the retrosynthetic strategy described in Scheme 4.11.



Scheme 4.11

In the first part of the strategy, 1,2-dihydronaphthalenes are synthesised from commercial α-tetralones. This can be performed through a two-step reduction and dehydration process. In the next step, chirality is induced through an asymmetric aziridination. Testing of various catalysts, modified upon known procedures, will be the major focus in this part of the thesis. Further, ring-opening of the aziridine and finally an *N*-deprotection, should liberate the substituted (*S*)-2-aminotetralin derivatives.

The target molecules for the strategy were 2-aminotetralin and the 6- or 7-methoxy substituted analogues, shown in Figure 4.2.



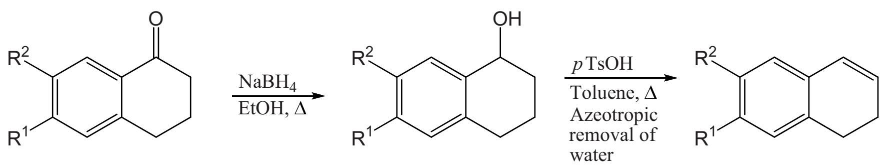
(*S*)-2-Aminotetralin (**94**) (*S*)-2-Amino-7-methoxytetralin (**27**) (*S*)-2-Amino-6-methoxytetralin (**96**)

Figure 4.2: Target molecules

4.3 Results and discussions

4.3.1 Synthesis of 1,2-dihydronaphthalenes

Substituted 1,2-dihydronaphthalenes were synthesised from their respective α-tetralones, all commercially available. The two-step reaction involves a reduction to an alcohol with $NaBH_4$ followed by an acid catalysed dehydration reaction, which is based on a procedure described by Hauser and Prasanna (Scheme 4.12).[185]



50: R^1=H, R^2=H
51: R^1=MeO, R^2=H
52: R^1=H, R^2=MeO

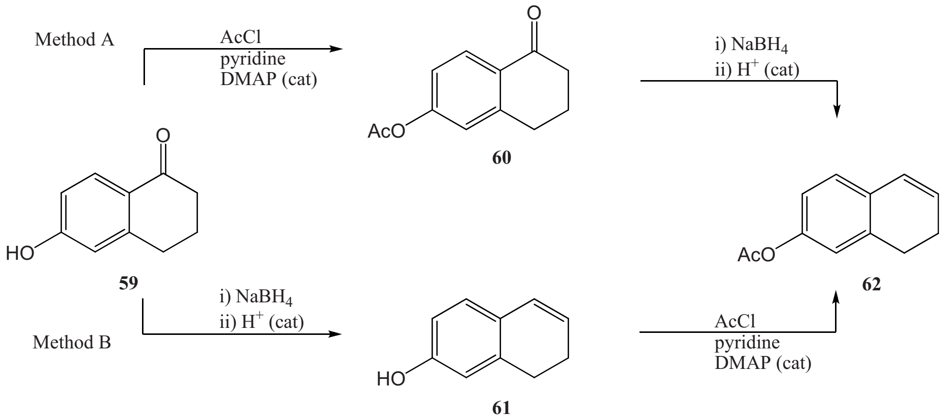
53: R^1=H, R^2=H
54: R^1=MeO, R^2=H
55: R^1=H, R^2=MeO

56: R^1=H, R^2=H
57: R^1=MeO, R^2=H
58: R^1=H, R^2=MeO

Scheme 4.12

The 1,2-dihydronaphthalenes **56**, **57** and **58** were synthesised in 76%, 90% and 97% yield, respectively.

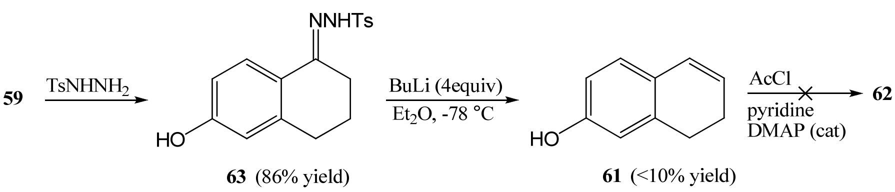
In the attempts to perform an asymmetric aziridination reaction on 6-methoxy-1,2-dihydronaphthalene (**57**), we encountered some problems. They will be discussed in detail in chapter 4.3.3, but the outcome resulted in the synthesis of another 6-substituted analogue of compound **57**. We decided to synthesise the 6-acetoxy analogue **62** from commercially available alcohol **59**. Two strategies were evaluated, differing only in the order of the acylation reaction, prior or after the two-step transformation. Both methods were attempted (Scheme 4.13).



Scheme 4.13

Initial tests demonstrated that method A was the only successful approach, since method B failed to provide any product. However, several improvements in method A were also found to be necessary due to low yield. This was mainly ascribable to the reduction/dehydration conditions, since acyltetralone **60** was formed in almost quantitative yield. After replacing *p*-toluenesulfonic acid by the weaker oxalic acid (*p*TsOH: pK_a -2.8, oxalic acid: pK_{a1} 1.25[186]), and changing the solvent from toluene to benzene, a yield of 37% was obtained for 6-acetoxy-1,2-dihydronaphthalene (**62**).

An alternative approach towards compound **62** was performed by utilising the Shapiro reaction.[187] By reacting the tetralone **59** with tosylhydrazin in refluxing ethanol, the tosylhydrazone **63** was isolated in 86% yield following a procedure by Baldwin and Krauss.[188] Unfortunately, the Shapiro reaction, i.e. synthesis of **61**, proved to be rather unsuccessful (Scheme 4.14).

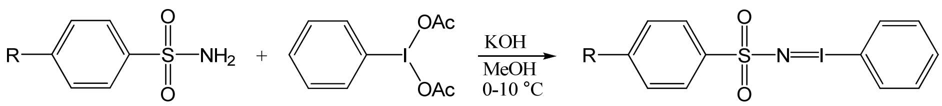


Scheme 4.14

Both diethyl ether and THF were attempted as solvents in the synthesis of **61**, but neither provided any products in good yields. Acylation of **61** resulted in a number of different products according to TLC, thus we decided to terminate any further attempts with the Shapiro reaction.

4.3.2 Preparation of [N-(arenesulfonyl)imino]phenyliodinanes

Three various nitrene precursors in the class of [N-(arenesulfonyl)imino]phenyl-iodinanes were synthesised, following a modified procedure described by Brandt and co-workers (Scheme 4.15).[178]



64: R = CH_3
65: R = NO_2
66: R = OCH_3

57

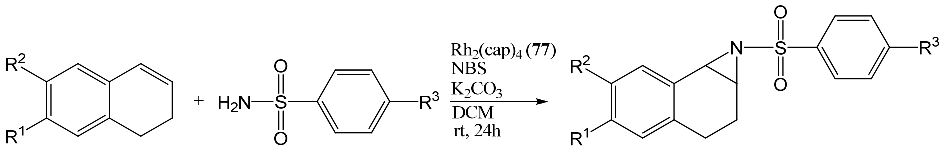
68: R = CH_3 (90% yield)
69: R = NO_2 (99% yield)
70: R = OCH_3 (68% yield)

Scheme 4.15

In these reactions, the products gradually crystallised out of the cold crude mixture, and they were finally washed with cold methanol. Following the original procedure by Yamada and co-workers, introducing water to the crude mixtures significantly lowered the yields (**68**: 62%, **69**: 72%, **70**: 38%).[170]

4.3.3 Racemic aziridination by rhodium catalysts

Racemic aziridines were prepared for chiral analysis purposes according to Doyle's $Rh_2(cap)_4$/NBS/$TsNH_2$ protocol.[183] A summary of the results are presented in Scheme 4.16 and Table 4.1.



56: R^1 = H, R^2 = H
57: R^1 = OMe, R^2 = H
58: R^1 = H, R^2 = OMe
62: R^1 = OAc, R^2 = H

64: R^3 = Me
65: R^3 = NO_2
66: R^3 = OMe

71: R^1 = H, R^2 = H, R^3 = Me
72: R^1 = H, R^2 = H, R^3 = NO_2
73: R^1 = H, R^2 = H, R^3 = OMe
74: R^1 = OMe, R^2 = H, R^3 = Me
75: R^1 = H, R^2 = OMe, R^3 = Me
76: R^1 = OAc, R^2 = H, R^3 = Me

Scheme 4.16

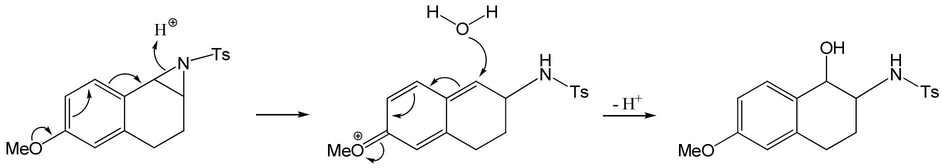
Table 4.1: Synthesis of racemic aziridines

Entry	Substrate	$ArSO_2NH_2$	Product	Yield (%)
1	**56**	**64**	**71**	92
2	**56**	**65**	**72**	30
3	**56**	**66**	**73**	76
4	**57**	**64**	**74**	4[a]
5	**58**	**64**	**75**	54
6	**62**	**64**	**76**	63

a) Isolated as a mixture with other products.

Suitable chiral HPLC-systems for the analytical separation of aziridine enantiomers (**71-76)** were developed, and implemented in the work of asymmetric aziridinations.

One result that strongly deviated from the others was the aziridination of the methoxy substituted substrate **57** (Entry 4). The reaction was monitored and showed a full conversion prior to the column chromatography, but only a small impure amount of aziridine **74** was isolated. A plausible explanation can be ascribed to the electron donating methoxy group in the 6-position, which may contribute to resonance stabilisation of the benzylic carbocation that is formed in the aziridine ring opening. Compared to aziridine **75** (Entry 5), with the methoxy group in the 7-position, no conjugated stabilisation of the carbocation is possible. Scheme 4.17 illustrates this theory in a ring opening mechanism, which eventually adds a molecule of water or alternatively another nucleophile present in the reaction mixture to provide the intermediate carbocation.

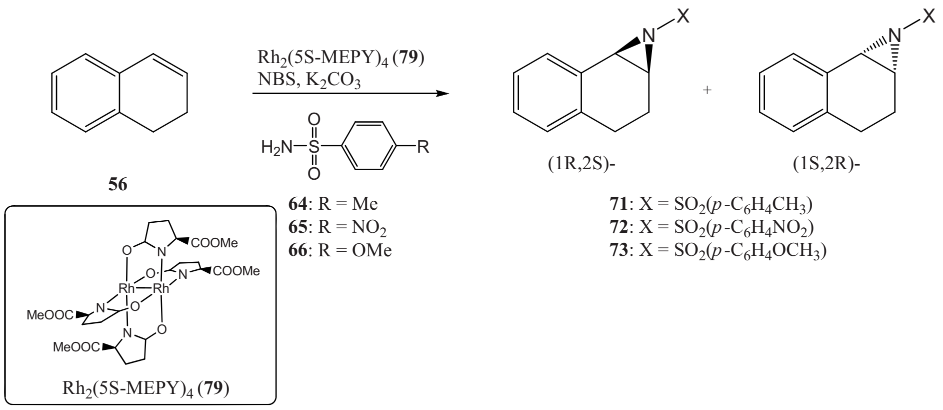


74

Scheme 4.17

To circumvent this stability problem, we decided to synthesise the aziridine analogues **76** and **84** (see Scheme 4.21 for structures), equipped with an acetoxy substituent on the expense of the methoxy. This was based on the prediction that an electron withdrawing group like acetoxy would not stabilise the ring opened carbocation like the one described in Scheme 4.17. Another factor was the possibility of transforming the acetoxy- into a methoxy-function, in the final 2-aminotetralin product **96** (Figure 4.2).

Synthesis of enantioenriched aziridines were attempted using one of Doyle's chiral dirhodium catalysts, i.e. Rh_2(5*S*-MEPY)$_4$ (**79**). As for the synthesis of racemic aziridines, we decided to test the same protocol, but utilising this chiral catalyst.[183] Scheme 4.18 and Table 4.2 summarises the results of these reactions.



Scheme 4.18

Table 4.2: Asymmetric aziridination catalysed by a chiral dirhodium complex

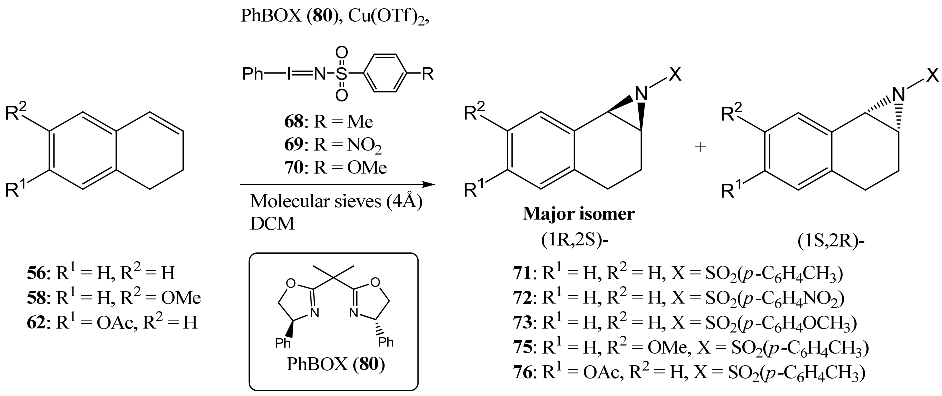
Entry	$ArSO_2NH_2$	Temp (ºC)	Time (h)	Product	Yield[a] (%)	% ee[b]
1	**64**	20	18	**71**	90	0
2	**64**	-20	72	**71**	56	0
3	**64**	-78	96	**71**	50	0
4	**65**	20	18	**72**	60	0
5	**66**	20	18	**73**	47	0

a) Isolated yield from column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.

The aziridination protocol provided no enantiomeric excess.

4.3.4 Copper catalysed asymmetric aziridination

Asymmetric aziridination of various alkenes were attempted with the bidentate ligand PhBOX (**80**) and $Cu(OTf)_2$ as catalyst, following Evans procedure.[172] The reaction was performed at different temperatures and with three types of nitrene donors **68**-**70** (Scheme 4.19, Table 4.3).



Scheme 4.19

Table 4.3: Asymmetric aziridination by PhBOX (**80**)/$Cu(OTf)_2$ catalysis

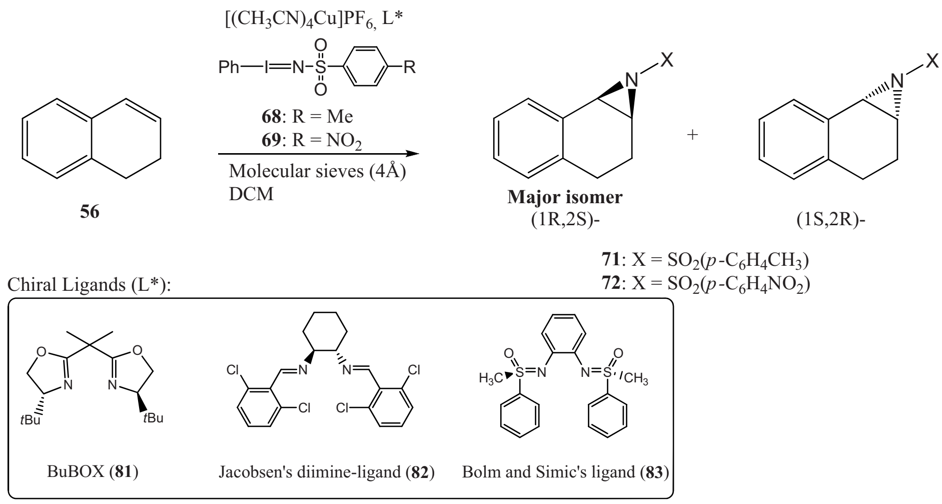
Entry	Substrate	Nitrene precursor	Temp (ºC)	Time (h)	Product	Yield[a] (%)	% ee[b]
1	**56**	**68**	20	36	**71**	16	30
2	**56**	**69**	20	36	**72**	26	37
3	**56**	**70**	20	36	**73**	22	36
4	**56**	**68**	-20	72	**71**	22	36
5	**56**	**69**	-20	72	**72**	16	16
6	**56**	**69**	-78	96	**72**	16	41
7	**58**	**68**	20	36	**75**	-[c]	-
8	**58**	**68**	-20	72	**75**	-[c]	-
9	**62**	**68**	-20	72	**76**	-[d]	-

a) Isolated yield after column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.
c) Only 2-methoxynaphthalene was identified as product from the reaction.
d) No reaction observed.

Table 4.3 shows that only the unsubstituted alkene **56** gave the corresponding aziridine utilising PhBOX as a chiral ligand, however in quite low yield. The enantiomeric excess was also relatively moderate (Entry 1-6, 16-26% yield, 16-41% ee). These were quite discouraging results, compared to other substrates published by Evans and co-workers, where the same protocol (PhBOX (**80**)/$Cu(OTf)_2$) was used.[172] In general they reported higher yields (60-76%) as well as higher enantioselectivity (>90% ee) for the aziridination reactions of unfunctionalised olefins. The 7-methoxy substituted alkene **58** underwent a different reaction (Entries 7 and 8), resulting in an aromatised naphthalene, i.e. 2-methoxynaphthalene. In the case of 6-acyl alkene **62** (Entry 9), no reaction took place.

In another series of asymmetric aziridinations, following Jacobsen's procedure,[177] various chiral ligands were tested, i.e. *t*-BuBOX (**81**), Jacobsen's diimine ligand **82** and Bolm and Simić's ligand **83** (Scheme 4.20). The latter ligand **83** has previously not been reported in aziridination attempts. In copper catalysed asymmetric hetero-Diels-Alder reactions however, excellent yields and selectivities have been reported.[189] Based on this, we decided to test it in parallel to the well known Evans and Jacobsen's catalytic systems. In addition to variations in reaction conditions, alternative copper-salts were tested, i.e. $[(CH_3CN)_4Cu]PF_6$ (simplified form is $[Cu]PF_6$), as well as the previously used copper triflate. The results of these experiments are shown in Scheme 4.20 and Table 4.4.

The best results were provided by a catalytic system with Jacobsen's diimine ligand **82**, $[Cu]PF_6$ and nitrene precursor **68** (Entry 1-4). Isolated yields up to 82% were obtained, with enantioselectivity values up to 87% ee. Through further recrystallisation, excellent enantiopurity was achieved (up to 98% ee). Attempts with Bolm and Simić's ligand **83** (Entry 5-6) failed to provide a decent yield (10-14%), and BuBOX **81** resulted only in traces of product. Switching to copper(II)triflate in combination with ligand **81** or **83** was also completely unsuccessful (Entry 8-10). Finally, changing the nitrene precursor from tosyl **68** to nosyl **69** (Entry 11-12), gave low yields ranging from 33 to 36%.



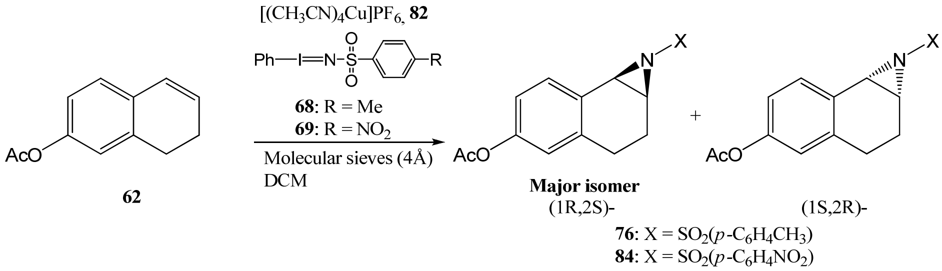
Scheme 4.20

Table 4.4: Copper catalysed asymmetric aziridination of **56** with various ligands

Entry	Nitrene precursor	Cu salt	L*	Temp (ºC)	Time (h)	Prod	Yield[a] (%)	% ee[b]
1	**68**	$[Cu]PF_6$	**82**	-40	24	**71**	47	75
2	**68**	$[Cu]PF_6$	**82**	-40	48	**71**	82, 47[c]	87, 98[c]
3	**68**	$[Cu]PF_6$	**82**	-20	24	**71**	63, 31[c]	65, 98[c]
4	**68**	$[Cu]PF_6$	**82**	-40	72	**71**	63	75
5	**68**	$[Cu]PF_6$	**83**	-40	24	**71**	10	17[e]
6	**68**	$[Cu]PF_6$	**83**	-20	48	**71**	14	14[e]
7	**68**	$[Cu]PF_6$	**81**	-40	48	**71**	traces	-
8	**68**	$Cu(OTf)_2$	**81**	-20	24	**71**	traces	-
9	**68**	$Cu(OTf)_2$	**81**	-40	48	**71**	-[d]	-
10	**68**	$Cu(OTf)_2$	**83**	-40	48	**71**	-[d]	-
11	**69**	$[Cu]PF_6$	**82**	-40	24	**72**	33	53
12	**69**	$[Cu]PF_6$	**82**	-20	24	**72**	36	34

a) Isolated yield after column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.
c) Isolated yield/% ee after crystallisation from EtOAc.
d) No reaction observed.
e) Abs. configuration (1S,2R)-for major isomer.

The best conditions from the results above were tested for the acetoxy substituted alkene **62**. These results are presented in Scheme 4.21 and Table 4.5.



Scheme 4.21

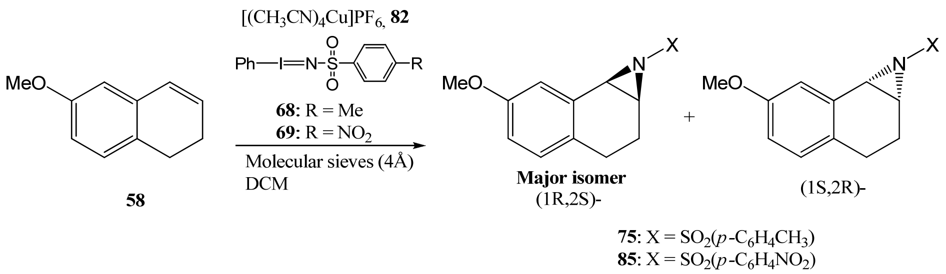
Table 4.5: Asymmetric aziridination of 6-acetoxy-3,4-dihydronaphthalene (**62**)

Entry	Nitrene precursor	Temp (°C)	Time (h)	Prod	Yield[a] (%)	% ee[b]
1	**68**	-40	24	**76**	6	63
2	**68**	-20	48	**76**	56	55
3	**68**	-40	48	**76**	39, 31[c]	60, 66[c]
4	**69**	-40	48	**84**	21	35

a) Isolated yield after column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.
c) Isolated yield/% ee after crystallisation from EtOH.

A moderate yield of 56% was obtained when utilising nitrene precursor **68**, and enantiomeric enrichment through recrystallisation proved to be more difficult for compound **76** (Entries 2-3). Nitrene precursor **69** did not improve the reaction outcome either (Entry 4).

Similar experiments were performed on 7-methoxy alkene **58**. The results from these experiments are shown in Scheme 4.22 and Table 4.6.



Scheme 4.22

Table 4.6: Asymmetric aziridination of 7-methoxy-3,4-dihydronaphthalene (**58**)

Entry	Nitrene precursor	Temp (ºC)	Time (h)	Prod	Yield[a] (%)	% ee[b]
1	**68**	-20	48	**75**	53	64
2	**69**	-20	48	**75**	24[d]	45[d]
3	**68**	-40	48	**75**	33	66
4[c]	**68**	-40	48	**85**	34	50

a) Isolated yield after column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.
c) Large scale experiment (5.6 mmol **58**) with half the amount of catalyst (5 mol %).
d) Recrystallisation from EtOAc/*n*-hexane afforded **75** in 13% yield and 5% ee. Concentration of the filtrate yielded enantiomerically enriched **75** (91% ee) in 10% yield.

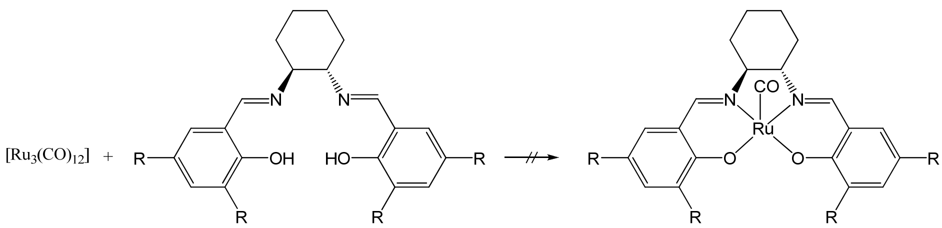
Analogue to previous results, nitrene precursor **69** provided lower yields and enantioselectivity compared to **68** (Entry 1 and 2). The result of the asymmetric synthesis of aziridine **75** is comparable with the one described for aziridine **76** (Table 4.2, Entry 2). Attempts to increase the ee of the products through recrystallisation of **75**, also failed.

The configurations given in chapter 4.3.4 are based on analysis of the applied catalyst, and by comparing the stereochemical results obtained with substrates **56** and **58** affording aziridines **71**[176] and **75** with known configuration. Abs. configuration for **75** was established by chemical correlation with the known trifluoroacetylaminotetralin **39** (see Chapter 4.3.7).[91]

4.3.5 Asymmetric aziridination by ruthenium catalysts

Inspired by the results from Katsuki's ruthenium(salen)CO complexes[180] presented in chapter 4.1.3, we decided to test similar complexes in the aziridination of alkene **56**. However, Katsuki's ruthenium complexes are not commercially available and they appear to be quite labour intensive to synthesise. Therefore we decided to test simpler ruthenium complexes equipped with substituted benzene rings, compared to Katsuki's substituted binaphthyl system.

Complexes **88** and **89** were attempted synthesised by reacting $Ru_3(CO)_{12}$ with the respective chiral ligands H_2[3,5-Cl_2-salen] (**86**) and H_2[3,5-*t*Bu_2-salen] (**87**), utilising the method described by Katsuki and co-workers (Scheme 4.23, Table 4.7).[180]



Scheme 4.23

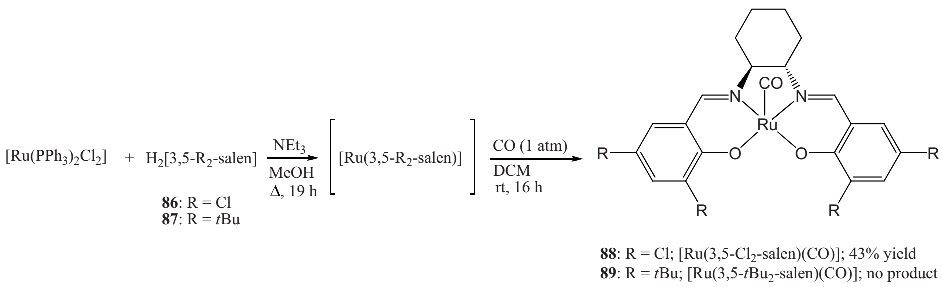
Table 4.7: Preparation of Ru-complex **88** and **89** by Katsuki's method

Entry	Ligand	Product	Ligand/ $Ru_3(CO)_{12}$[a]	Solvent	Time (d)	Yield[b]
1	**87**	**89**	0.67 : 1	EtOH	1	-
2	**86**	**88**	0.74 : 1	EtOH	2	-
3	**86**	**88**	0.72 : 1	Toluene	1	-
4	**86**	**88**	1 : 1	EtOH	2	-
5	**86**	**88**	2.5 :1	EtOH	5	-

a) Ratio ligand: $Ru_3(CO)_{12}$.
b) No yield provided.

All five experiments (Entry 1-5) all failed to provide the target complexes **88** and **89**, respectively. Variations in the ligand/Ru-source ratio, changing to dried solvent quality and longer reaction times were totally unsuccessful.

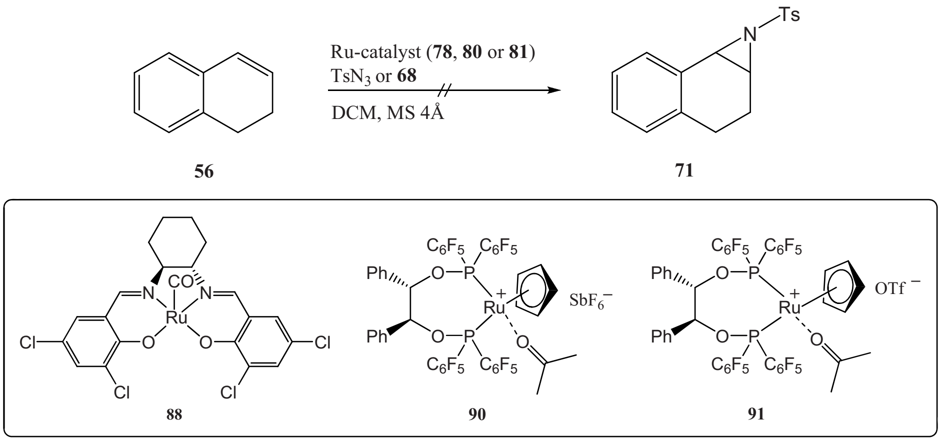
Another synthetic approach towards the formation of complexes **88** and **89** was investigated. The methodology was based on Che's method, which consists of a two step process.[190] First, the salen ligand (**86** or **87**) was reacted with a ruthenium(II) source ([Ru(PPh_3)$_2$(Cl)$_2$]) under basic conditions (Et_3N). Second, the crude mixture was treated with CO-gas, to introduce the CO-ligand (Scheme 4.24).



Scheme 4.24

While we were able to synthesise **88** in a yield of 43% (Che and co-workers reported 66% yield), attempts to prepare the *t*Bu analogue **89** was unsuccessful. The latter has not been reported in literature either.

Asymmetric aziridination of alkene **56** with three various Ru-catalysts were attempted, based on Katsuki's procedure.[180] As a nitrene precursor, *p*-toluenesulfonyl azide (TsN_3) was used (except for Entries 3 and 4, where **68** was used). This precursor was prepared from *p*-toluenesulfonyl chloride and NaN_3 by a method published by Ghosh and co-workers.[191] Beside complex **88**, which is already described thoroughly, we decided to test two other Ru-complexes (**90** and **91**) currently available within the research group. Previously, these Lewis acid catalysts have been tested in asymmetric Diels-Alder reactions between enals and dienes.[192] These two complexes are also chiral, unsaturated 16-electron Ru-complexes, if we consider acetone to be only loosely coordinated to the metal centre. Scheme 4.25 and Table 4.8 summarises the asymmetric aziridination experiments catalysed by the various ruthenium-complexes.



Scheme 4.25

Table 4.8: Asymmetric aziridination by chiral Ru-catalysts

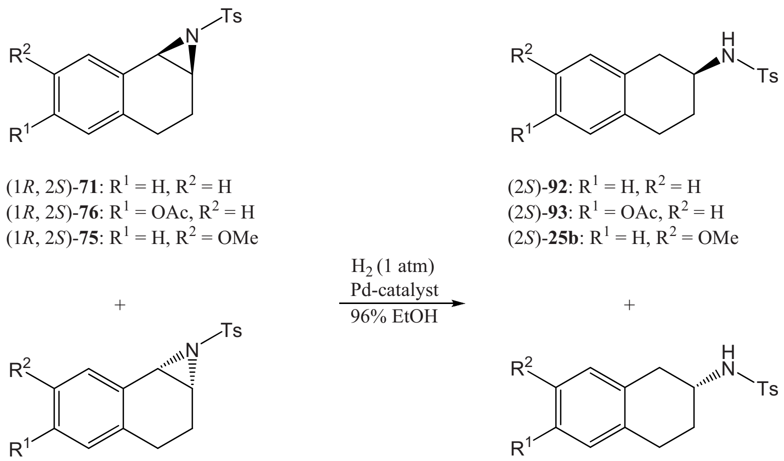
Entry	Ru-catalyst	Nitrene donor	Time (h)	Product **71**
1	**90**	TsN_3	24	-
2	**91**	TsN_3	24	-
3	**90**	PhI=NTs (**68**)	48	-
4	**91**	PhI=NTs (**68**)	48	-
5	**88**	TsN_3	24	-
6	**88**	TsN_3	48	-

Unfortunately, non of the catalytic systems (Entry 1-6) provided the desired aziridine derivative **71**. The two ruthenium catalysts **90** and **91** were tested primarily due to availability, and exist in a quite different geometry and electronic configuration compared to Katsuki's salen-complexes.[180] Negative results in Entry 1-4 were easily accepted based on modest expectations, since no such structurally related Ru-compounds have been reported in aziridination reactions. On the other hand, catalyst **88** can be considered to be a simplified version of Katsuki's complex, where disubstituted phenyl rings are replaced by monosubstituted binaphthyls. This substitution pattern should not dramatically alter the electronic properties of the metal, and based on this we expected **88** as a potential catalyst in the aziridination reaction (Scheme 4.25). Analyses of the reactions (Entries 5-6) showed that no reaction occurred. This might indicate that activation through higher temperature or UV-irradiation is necessary to initiate the reaction. However, compared to the results by Katsuki and co-workers, such activation should not be required. Another question is the choice of solvent. While DCM was the solvent of choice for Katsuki's aziridinations, complexes **88**, **90** and **91** were sparingly soluble in DCM. This difference can be ascribed to the larger organic binaphthyl moieties in Katsuki's complex, resulting in a higher DCM solubility.

4.3.6 Ring opening reactions of aziridines by catalytic hydrogenation

The aziridines **71**, **75** and **76** were ring opened by a procedure developed by Tanner and Gautun,[63] in which the aziridine ring is subjected to hydrogenolysis of the benzylic *C*-*N* bond. The reaction is highly regioselective because of the potential of carbocation/radical stabilisation in the benzylic position. Scheme 4.26 and Table 4.9 summarises the results of the ring opening reactions.

The results of the catalytic hydrogenations (Entry 1-6) demonstrate clearly that these reactions are both clean and regioselective. In all cases, almost quantitative yields were obtained after a simple filtration of the crude mixture. Based on the results obtained for (1*R*, 2*S*)-**76** (Entry 4), we decided to terminate our work towards target molecule **96**.



(1*R*, 2*S*)-**71**: R^1 = H, R^2 = H
(1*R*, 2*S*)-**76**: R^1 = OAc, R^2 = H
(1*R*, 2*S*)-**75**: R^1 = H, R^2 = OMe

\+

(1*S*, 2*R*)-**71**: R^1 = H, R^2 = H
(1*S*, 2*R*)-**76**: R^1 = OAc, R^2 = H
(1*S*, 2*R*)-**75**: R^1 = H, R^2 = OMe

(2*S*)-**92**: R^1 = H, R^2 = H
(2*S*)-**93**: R^1 = OAc, R^2 = H
(2*S*)-**25b**: R^1 = H, R^2 = OMe

\+

(2*R*)-**92**: R^1 = H, R^2 = H
(2*R*)-**93**: R^1 = OAc, R^2 = H
(2*R*)-**25b**: R^1 = H, R^2 = OMe

Scheme 4.26

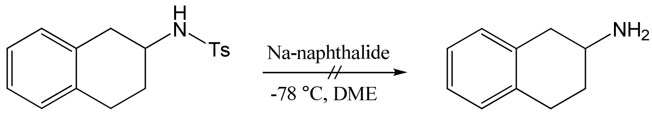
Table 4.9: Ring opening of aziridines by catalytic hydrogenation

Entry[a]	Aziridine (% ee)	Time (h)	Product	Yield[b] (%)	% ee[c]
1	(rac)-**71**	1	(rac)-**92**	95	-
2	(1*R*, 2*S*)-**71** (98% ee)	1	(2*S*)-**92**	99	98
3	(rac)-**76**	0.5	(rac)-**93**	99	-
4	(1*R*, 2*S*)-**76** (55% ee)	0.5	(2*S*)-**93**	97	45
5	(rac)-**75**	0.5	(rac)-**25b**	97	-
6	(1*R*, 2*S*)-**75** (56% ee)	0.5	(2*S*)-**25b**	98	60

a) 10 mol % catalyst (Pd/C) were used in all reactions.
b) Isolated yield after column chromatography.
c) The enantiomeric excess of the products was determined by HPLC.

4.3.7 Deprotection of tosyl amides

In order to achieve our target amines **94** and **27**, we needed to remove the tosyl protecting groups. Our first attempt was done by a Tanner and Somfai protocol, utilising excess sodium naphthalide as a one electron reductant (Scheme 4.27).[193]

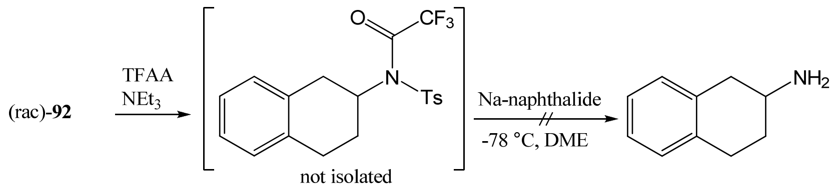


(rac)-**92** (rac)-**94**

Scheme 4.27

Unfortunately, no reaction was observed under these conditions. This might be due to non-satisfactory dryness of our reaction conditions. A deep blue/green colour induced by the naphthalide anion should be present during the progress of the reaction, but in this case the solution turned yellow after the addition of tosylamide **92**.

In a second approach, the reaction was attempted via a reactive secondary tosylamide, prior to the reaction with Na-naphthalide. This was performed by reacting **92** with TFAA under basic conditions, following a procedure by Moussa and Romo.[194] The bis-protected intermediate, was not isolated, but used directly (Scheme 4.28).

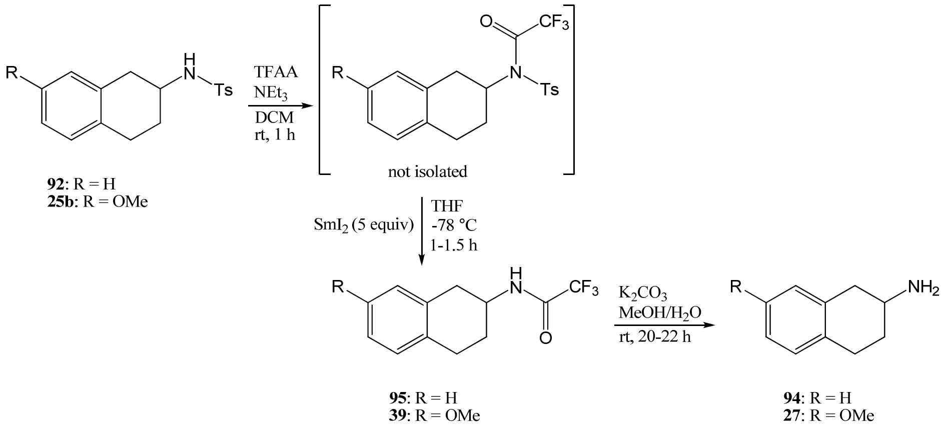


(rac)-**94**

Scheme 4.28

Again we were not able to liberate the amine function, and the sodium naphthalide approach was terminated.

In a third approach we tested the Moussa and Romo protocol, where samarium(II)iodide is used as a mild and efficient one electron reducing agent.[194] Again, an intermediate reactive bis-protected amine was prepared in situ by a reaction with TFAA, followed by the addition of the reducing agent (Scheme 4.29 and Table 4.10).



Scheme 4.29

Table 4.10: Removal of the tosyl protecting groups

Entry	Tosylate (% ee)	Product	Yield[a] (%)	% ee[b]
1	(2*S*)-**92** (98)	(2*S*)-**95**	82	98
2	(2*S*)-**25b** (56)	(2*S*)-**39**	85	56

a) Isolated yield after column chromatography.
b) The enantiomeric excess of the products was determined by HPLC.

The reductive conditions successfully removed the tosyl moiety, resulting in the formation and isolation of trifluoroacetamides **95** and **39**. The base labile protection group was successively removed by aqueous base treatment with K_2CO_3 in up to quantitative yields ((2*S*)-**94**: 81% yield and (2*S*)-**27**: >99% yield), following a procedure by Gómez-Sánches and co-workers.[151]

Finally, in a very recent publication by Ankner and Hilmersson, the deprotection takes place without the need of preparing the intermediate bis-protected amine. In this procedure, samarium(II)iodide instantly deprotects and liberates the free amine.[137] Results from utilising this protocol have already been presented in chapter 2.3.9.

4.4 Summary

Three 1,2-dihydronaphthalene derivatives were successfully synthesised as substrates for the asymmetric aziridinations in up to 97% yield. The 6-methoxy isomer **57** was replaced by the 6-acetoxy isomer **62**, since we were not able to produce 6-methoxy-aziridine **74**.

Synthesis of racemic aziridines **71**-**76** were performed according to Doyle's $Rh_2(cap)_4$/NBS/$TsNH_2$ protocol. We were able to obtain acceptable yields (30-92%) for the purpose of analytical references (HPLC analyses of % ee). The very same reaction protocol was also tested with the chiral dirhodium catalyst Rh_2(5*S*-MEPY$)_4$, only to provide racemic mixtures (47-90% yield).

Asymmetric aziridination attempts with various copper sources ($Cu(OTf)_2$ and $[(CH_3CN)_4Cu]PF_6$), ligands (Evans bis(oxazolines), Jacobsen's diimines and Bolm and Simić's ligand) and nitrene precursors ([*N*-arenesulfonyl)imino]phenyliodinanes) were attempted. We were able to obtain up to 82% yield (87% ee) for the non-substituted alkene **56** (98% ee after recrystallisation), but only low to mediocre aziridination yields were achieved for 6-acetoxy-alkene **62** (6-39%, 35-63% ee) and 7-methoxy-alkene **58** (24-53%, 45-66% ee).

Three ruthenium ligands were also tested in asymmetric aziridination according to a protocol by Katsuki. Unfortunately these systems were unable to deliver any products.

Ring opening of aziridines by catalytic hydrogenation was performed smoothly in high yields (>95%). Improved methods for the deprotection of *N*-tosyl groups, under mild conditions, provided good yields (up to 85%) in the final step.

To reach the goal of establishing an efficient catalytic system for asymmetric aziridination of substituted 1,2-dihydronaphthalenes, new catalysts should be evaluated.

4.5 Experimental

The full experimental description for Chapter 4 is reported in Paper III.

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Appendices

Paper I

Aaseng, J. E. and Gautun, O. R.

Synthesis of substituted (*S*)-2-aminotetralins via ring-opening of aziridines prepared from L-aspartic acid β-*tert*-butyl ester.

Tetrahedron, **2010**, *66*, 8982-8991.

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Paper II

Aaseng, J. E. and Gautun, O. R.

Synthesis of (*S*)-2-amino-7-methoxytetralin and isoindolo[1,2-a]isoquinolinone derivatives from L-aspartic acid.

Manuscript.

Graphical Abstract

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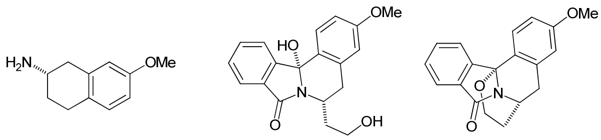

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Synthesis of (*S*)-2-amino-7-methoxytetralin and isoindolo[1,2-a]isoquinolinone derivatives from L-Aspartic acid

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ABSTRACT

This paper describes a new total synthesis for (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT,** from L-aspartic acid in an overall yield of 11% over nine steps. The major loss was ascribed to a key intramolecular Friedel-Crafts cyclisation step, which afforded up to 36% yield. Attempts to perform Friedel-Crafts cyclization of an intermediate phthalimide protected amino alcohol **13** did not give the desired protected **(*S*)-7-MeO-AT**. On the other hand, two new isoindolo[1,2-a]isoquinolinone derivatives **14** and **15,** were isolated in 11 and 21% yield, respectively.

1. Introduction

The pharmacological activity of 2-aminotetralin (2-amino-1,2,3,4-tetrahydronaphthalene, AT) was first described by Bamberger and Filehne in 1889.[1] Since then a large number of articles and patents, mostly describing studies of the physiological properties of this class of compounds, have appeared.[2]

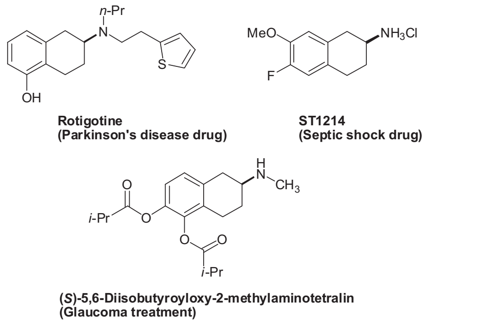
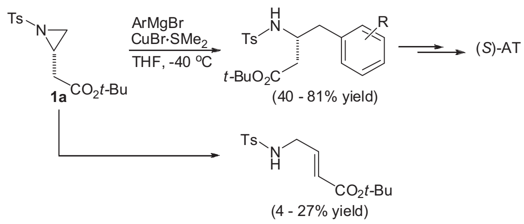


Fig. 1. Pharmacological active 2-aminotetralins.

Today, several enantiopure ATs are used in the treatment of medical conditions like Parkinson's disease,[3] glaucoma[4] and septic shock[5,6] (Fig. 1).

Recently, we reported the synthesis of substituted (*S*)-ATs via ring-opening of aziridine **1a** prepared from L-aspartic acid β-*tert*-butyl ester (see Scheme 1).[7] Unfortunately, this protocol was accompanied with a disturbing elimination reaction. In order to circumvent this side reaction we have tested an alternative chiral C_4-aziridine building block, **1b**, as shown in the protocol described in Scheme 2.



Scheme 1.

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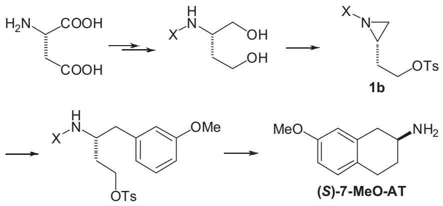


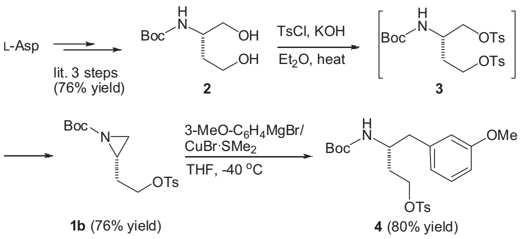
Scheme 2. Strategy for enantioselective synthesis of (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT**, from L-aspartic acid.

In the presented study (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT**, was chosen as the target molecule. The protocol does, however, have the potential to offer ATs with other subtstiutents on the aromatic ring.

2. Results and discussion

2.1. Preparation and ring-opening of aziridine 1b

Natural L-aspartic acid (L-Asp) served as starting material in a three step synthesis to *N*-Boc-diol **2**, following literature procedures (Scheme 3).[8,9] Ring-closing of *N*-Boc-diol **2** to aziridine **1b** was performed according to an adopted procedure described by Wessig and Schwartz.[10] In addition to the intermediate ditosylate **3**, the reaction afforded **1b** as the only cylized product. This observation was a contrast to the tosylated (or mesylated) *N*-Boc-β-amino alcohols tendency to form oxazolinones.[11,12] We were not able to observe any azetidine formation either, which might occur in some cases where three- and four-membered ring formation are competitive pathways.[13]

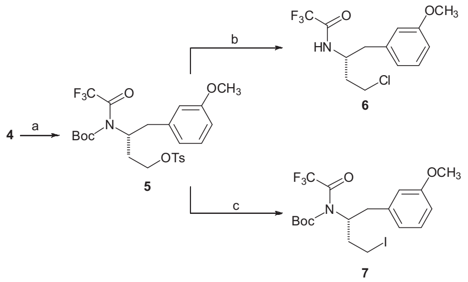


Scheme 3.

Ring-opening reaction of *N*-Boc-aziridine **1b** by a copper aryl nucleophile {from (3-methoxyphenyl)magnesium bromide and CuBr·Me_2S} provided compound **4** in a decent yield. However, the product proved to be somewhat unstable at room temperature. Refluxing of **4** in THF and DCM for 6 hours gave 50% and 23% decomposition respectively. As a consequence, product **4** was stored in an inert atmosphere at −18 °C.

2.2. Intramolecular Friedel-Crafts alkylation

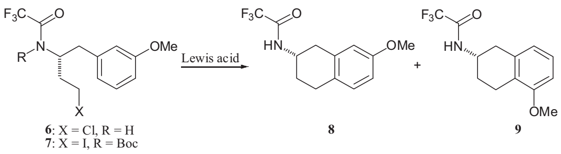
Little is known about the possibilities for intramolecular Friedel-Crafts alkylation of alkyl tosylates, or compounds holding other sulfone based leaving groups (e.g. mesyl or triflate). Initial efforts to ring-close tosylate **4** in the presence of $TiCl_4$ in DCM gave rapid cleavage of the Boc-group even at room temperature. No AT products were observed. A trifluoroacetyl group was therefore introduced to double protect the amine function in **4** (see Scheme 4). Attempted Friedel-Crafts cyclisation of **5** under the same conditions did, however, give cleavage of the Boc-group as well as halogen exchange of the tosyl group, resulting in chloride **6**. A similar exchange has been reported with oxophilic Lewis acids in the presence of alkyl tosylates.[14]



Scheme 4. (a) TFAA, Et_3N, DCM, 0 ºC – rt. 99% yield. (b) $TiCl_4$, DCE, 80 °C, 58% yield. (c) NaI, acetone, 35 °C, 12 h. 78% yield.

The newly formed alkyl chloride **6** could, however, serve as a substrate for a classical Friedel Crafts alkylation reaction. The corresponding iodide **7** was prepared for comparison (see Scheme 4). The results of the cyclisation reactions of chloride **6** and iodide **7** are summarised in Table 1.

Table 1. Intramolecular Friedel-Crafts alkylation



Entry	Substrate	Lewis acid	Conditions, solvent	Ratio [e] **8** : **9**	% yield **8**,[a] (% *ee*) [b]
1	**6**	$AlCl_3$ (2 equiv)	80 °C, 7 h DCE		- [c]
2	**6**	$AlCl_3$ (2 equiv)	83 ºC, 20 h DCE		- [c]
3	**6**	$InBr_3$ (2 equiv)	83 ºC, 20 h DCE	69 : 31	complex mixture
4	**6**	$AlCl_3$ (3 equiv)	100 ºC, 20 h, DCM [d]	83 : 17	36 (99)
5	**6**	$InBr_3$ (2 equiv)	80 ºC, 20 h DCM [d]	68 : 32	<15 (99)
6	**6**	$SnCl_4$ (3 equiv)	80 ºC, 20 h DCM [d]		- [c]
7	**6**	$BF_3·Et_2O$ (3 equiv)	80 ºC, 20 h DCM [d]		- [c]
8	**7**	$InBr_3$ (2 equiv)	80 ºC, 18 h DCM [d]	71 : 29	26 (97)

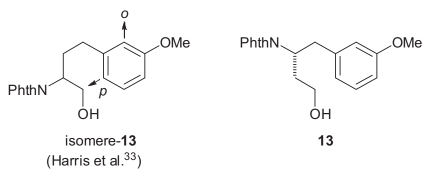
[a] Isolated yield after purification. [b] The enantiomeric excess of the products was determined by HPLC analysis. [c] No reaction. [d] Reaction performed in closed pressure tube. [e] Ratio determined according to ^1H NMR spectrum of the product mixture.

Two solvents and four Lewis acids were tested. Both, chloride **6** and iodide **7** afforded the desired target molecule **8**. Unfortunately, neither of them provided regioselective reactions, giving significant amounts of the 5-methoxy isomer **9** as well. We did not succeed in finding the optimal conditions for the reactions. The best selectivity (ratio **8** : **9** = 83 : 17) and yield (36 % yield based on ^{1}H NMR of the product mixture) of **8** was obtained with $AlCl_3$ in DCM at 100 °C (closed glass pressure tube) for 20 hours (Table 1, entry 4). The products **8** and **9** were only partly separable by flash chromatography.

Target molecule **(*S*)-7-MeO-AT** is accessible through basic hydrolysis of **8**, by a procedure described by Gómez-Sánches *et al.*[15] Hydrolysis of trifluoroacetylated amines are reported to provide up to quantitative yields.

2.3. Preparation and cyclization of phthalimide protected amino alcohol 13

Harris *et al.*[16] have reported preparation of ATs by ring-closure of phthalimide protected isomere-**13** (see Fig. 2). Treatment of isomere-**13** with CF_3SO_3H in PhCl at 80 °C gave quantitive yield of ATs in an *ortho* : *para* ratio of 1 : 3. Inspired by their results, we aimed at preparing **(*S*)-7-MeO-AT** from the **13**, which was assumed to be available from **4**.

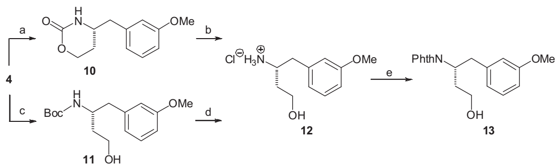


isomere-**13**
(Harris et al.[33])

13

Fig. 2 Phthalimide protected AT precursors.

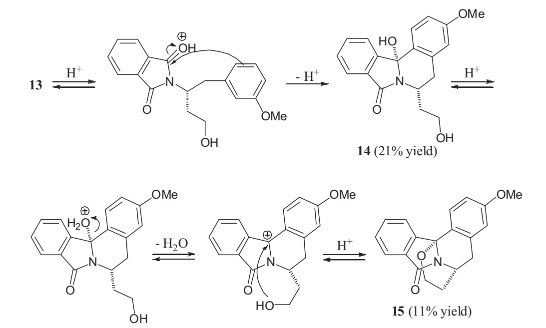
Synthesis of PhthN-alcohol **13** was successfully provided via two alternative routes, according to Scheme 5.



Scheme 5. (a) KOH, DMSO, rt, 18h, 60% yield. (b) (i) LiOH, MeOH/H_2O, 70 ºC, 2 h. (ii) EtOH/conc HCl, rt, 65% yield. (c) SmI_2, H_2O, pyrrolidine, rt, 5 min, 32% yield. (d). Conc HCl/toluene, 65 ºC, 2 h, yield 80% (e) Phthalic anhydride, Et_3N, toluene, Δ, 24 h, 43% yield.

Treatment of PhthN-alcohol **13** with triflic acid according to the procedure described by Harris *et al.*[16] gave a product mixture which did not appear to contain significant amounts of the desired **(*S*)-7-MeO-AT**. We were, however, able to isolate two main products **14** and **15**, shown in Scheme 6, which were structurally elucidated by NMR experiments (COSY, HSQC, HMBC, NOESY). A mechanistic suggestion for the formation of **14** and **15** is given in Scheme 6.

Compounds **14** and **15** can be classified in the isoindolo[1,2-a]isoquinolinone family. This family contains one known natural



Scheme 6. Suggested mechanism for the formation of compounds **14** and **15**.

product, i.e. (±)-nuevamine, isolated from *Berberis darwinii* Hook species.[17] Several approaches to synthesise derivatives of this class of compounds are known from literature.[18-21] Some of these compounds are considered to have potential biological activities.[22]

3. Conclusion

A new total synthesis for (*S*)-2-amino-7-methoxytetralin, **(*S*)-7-MeO-AT,** from L-aspartic acid has been developed. The applied protocol afforded protected **(*S*)-7-MeO-AT** in an overall yield of 11% over nine steps. The major loss occurred in the step involving the intramolecular Friedel-Crafts cyclisation, for which only up to 36% yield was obtained, partially due to problems with separation of regioisomeric products.

Attempts to perform Friedel-Crafts cyclization of the phthalimide protected alcohol **13** did not give the desired protected **(*S*)-7-MeO-AT**. On the other hand, this step afforded two new isoindolo[1,2-a]isoquinolinone derivatives **14** and **15**, in 11 and 21% yield, respectively.

4. Experimental

4.1. General

All reactions were performed under an argon or nitrogen atmosphere. Tetrahydrofuran (THF) was distilled under nitrogen atmosphere from Na/benzophenone. Dichloromethane was distilled under nitrogen from calicium hydride. Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F_{254} plates, using UV light at 312 nm and a 5% alcoholic molybdophosphoric acid for detection. Silica gel for flash chromatography was purchased from Merck. Optical rotations were measured with a Perkin-Elmer 241 Polarimeter. Enantiomeric excesses were determined by HPLC analysis, using Daicels column Chiralcel OJ (250 x 4.6 mm). ^{1}H and ^{13}C NMR spectra (Bruker Advance DPX instruments 300/75 MHz and 400/100 MHz) were obtained from solutions of $CDCl_3$, and chemical shifts are in ppm and referenced to TMS *via* the lock signal of the solvent. ^{1}H and ^{13}C NMR signals were assigned by 2D correlation techniques (COSY, HSQC, HMBC, NOESY). IR spectra were run on a Thermo Nicolet FT-IR NEXUS instrument, and only the strongest/structurally most important peaks are listed. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography.

4.2. Preparation and ring-opening of aziridine 1b

*4.2.1. (S)-tert-butyl 2-(2-tosyloxy)ethyl)aziridine-1-carboxylate (**1b**).*

The title compound was prepared by adopting a procedure described by Wessig and Schwartz.[10] Diol **2**[8,9] (2.42 g, 11.8 mmol) was dissolved in dry diethyl ether (180 mL) and added tosyl chloride (6.0 g, 31.5 mmol). Pellets of KOH (3.6 g, 65 mmol) were grinded and added instantly to the mixture. After 24 h of reflux, additional KOH (1.0 g, 18 mmol) was added. The reaction was quenched by pouring it over crushed ice (100 g). The organic layer was washed with brine (50 mL) and dried ($MgSO_4$). Purification by flash chromatography (15% EtOAc in *n*-pentane) provided 3.08 g of **1b** as a colorless oil (76 % yield). Data for **1b**: R_f = 0.39 (EtOAc/*n*-hexane, 1:2). $[\alpha]_D^{22}$ +19.3 (1.0, CH_2Cl_2). ^{1}H NMR (300 MHz): δ 7.80 (app d, *J* 8.0 Hz, 2H, tolyl), 7.35 (app d, *J* 8.0 Hz, 2H, tolyl), 4.25-4.12 (m, 2H, CH_2-O), 2.47-2.37 (m, 1H, CH-N), 2.45 (s, 3H, tolyl), 2.27 (d, *J* 6.0 Hz, 1H, C**H**H-N), 1.92 (d, *J* 3.6 Hz, 1H, CH**H**-N), 1.93-1.71 (m, 2H, C**H**$_2$-CH_2O), 1.43 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 162.1 (OC(=O)N), 144.9 (tolyl), 133.0 (tolyl), 129.9 (tolyl), 127.9 (tolyl), 81.4 (*t*-Bu), 68.0 (CH_2-O), 34.3 (CH-N), 31.9 (**C**H_2-CH_2O), 31.4 (CH_2-N), 27.9 (*t*-Bu), 21.6 (tolyl). IR (thin film, NaCl): 2979 (s), 1717 (s), 1598 (m), 1367 (s), 1309 (s), 1222 (s), 1121 (m) cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{23}NNaO_5S$ $(M+Na)^+$ 364.1189, found 364.1200.

*4.2.2. (R)-3-(tert-butoxycarbonylamino)-4-(3-methoxyphenyl)butyl 4-methylbenzenesulfonate (**4**).*

The title compound was made by adopting a procedure described by Burgaud and co-workers.[23] A solution of 3-bromoanisole (1.50 ml, 11.8 mmol) in anhydrous THF (8.5 mL) was added slowly to magnesium turnings (280 mg, 11.5 mmol) over a period of approximate 10 min. Once the addition was complete, the reaction was continued with vigorous stirring for 30 min, then titrated utilizing salicylaldehyde as a titration indicator,[24] and used immediately in the following reaction. A solution of Boc-aziridine **1b** (535 mg, 1.57 mmol) and CuBr·Me_2S (48 mg, 0.233 mmol, 15 mol %) in dry THF (25 mL) was cooled to −40 °C under argon atmosphere. To the solution, a standardized amount the Grignard solution (3.14 mmol, 2 equiv) was added over a period of 5 min. The reaction mixture was stirred for 2 h and allowed to warm to −10 °C. The reaction mixture was quenched by aqueous NH_4Cl (saturated, 30 mL), warmed up to room temperature and extracted with diethyl ether (4 x 50 mL). The combined organic layer was washed with brine and dried ($MgSO_4$). Purification performed by flash chromatography (15% EtOAc in *n*-pentane), yielded **4** (564 mg, 80%) as a white crystalline material. Data for **4**: Mp 74 - 77 °C (decomp. gas evolves), R_f = 0.33 (15% EtOAc in *n*-pentane). $[\alpha]_D^{22}$ −8.4 (1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.77 (app. d, *J* 8.0 Hz, 2H, tolyl), 7.33 (app. d, *J* 8.0 Hz, 2H, tolyl), 7.19 (app. t, *J* 7.8 Hz, 1H, H_{Ar}-5), 6.76 (app. dd, *J* 7.8, 2.6 Hz, 1H, H_{Ar}-4), 6.70 (app. d, *J* 7.8 Hz, 1H, H_{Ar}-6), 6.66 (app. s, 1H, H_{Ar}-2), 4.36 (d, *J* 8.4 Hz, 1H, NH), 4.15-4.02 (m, 2H, H-1), 3.85-3.76 (m, 1H, H-3), 3.78 (s, 3H, CH_3O), 2.85-2.76 (m, 1H, 1H, H-4), 2.69 (dd, *J* 13.2, 6.8 Hz, 1H, H-4), 2.44 (s, 3H, tolyl), 1.96-1.84 (m, 1H, H-2), 1.82-1.66 (m, 1H, H-2), 1.38 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 159.7 (C_{Ar}-3), 155.1 (OC(=O)N), 144.8 (tolyl), 139.0 (C_{Ar}-1), 132.9 (tolyl), 129.9 (tolyl), 129.5 (C_{Ar}-5), 127.9 (tolyl), 121.7 (C_{Ar}-6), 115.0 (C_{Ar}-2), 112.1 (C_{Ar}-4), 79.0 (*t*-Bu), 67.9 (C-1), 55.2 (CH_3O), 48.8 (C-3), 41.0 (C-4), 33.2 (C-2), 28.3 (*t*-Bu), 21.6 (tolyl). IR (KBr): 2929 (m), 1704 (s), 1600 (m), 1490 (s), 1392 (s), 1292 (s), 1175 (s), 1097 (m) cm^{-1}. HRMS (ESI) calcd for $C_{23}H_{32}NO_6S$ $(M+H)^+$ 450.1945, found 450.1946.

4.3. Intramolecular Friedel-Crafts alkylation

*4.3.1. (R)-3-(tert-butoxycarbonyl)-2,2,2-trifluoro-acetamido-4-(3-methoxyphenyl)butyl 4-methyl-benzenesulfonate (**5**).*

N-Trifluoroacetylation of tosylate **4** was performed according to a general protocol described by Moussa and Romo.[25] Tosylate **4** (450 mg, 1.00 mmol) was dissolved in DCM (20 mL) and cooled to 0 ºC, added Et_3N (280 μL, 2.01 mmol) followed by TFAA (280 μL, 2.01 mmol). After vigorous stirring for 2.5 h at room temperature, the volatiles were removed under reduced pressure. The crude mixture was dissolved in DCM (50 mL), washed with aqueous $NaHCO_3$ (saturated, 25 mL), aqueous citric acid (2% wt, 20 mL) and dried ($MgSO_4$). Removal of the solvent yielded **5** (541 mg, 99%) as a relatively pure colorless oil. Data for **5**: R_f = 0.37 (15% EtOAc in *n*-pentane). $[\alpha]_D^{23}$ +40.2 (1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.76 (app. d, *J* 8.4 Hz, 2H, tolyl), 7.33 (app. d, *J* 8.4 Hz, 2H, tolyl), 7.16 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.75 (app. dd, *J* 7.9, 2.2 Hz, 1H, H_{Ar}-4), 6.68 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.64 (app. s, 1H, H_{Ar}-2), 4.75-4.60 (m, 1H, H-3), 4.15-3.90 (m, 2H, H-1), 3.76 (s, 3H, CH_3O), 3.14 (dd, *J* 13.6, 10.4 Hz, 1H, H-4), 2.85 (dd, *J* 13.6, 6.0 Hz, 1H, H-4), 2.43 (s, 3H, tolyl), 2.40-2.29 (m, 1H, H-2), 2.11-2.00 (m, 1H, H-2), 1.39 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 160.5 (q, $^2J_{C,F}$ 39.2 Hz, N**C**(O)CF_3), 159.7 (C_{Ar}-3), 150.8 (Boc), 144.9 (tolyl), 138.2 (C_{Ar}-1), 132.7 (tolyl), 129.9 (tolyl), 129.6 (C_{Ar}-5), 128.0 (tolyl), 121.5 (C_{Ar}-6), 115.3 (q, $^1J_{C,F}$ 287.3, CF_3), 114.5 (C_{Ar}-2), 112.8 (C_{Ar}-4), 86.2 (Boc), 67.1 (C-1), 57.5 (C-3), 55.1 (CH_3O), 38.7 (C-4), 30.9 (C-2), 27.3 (Boc), 21.6 (tolyl). IR (thin film, NaCl): 2985 (m), 1758 (m), 1713 (m), 1600 (m), 1456 (m), 1398 (m), 1261 (m), 1144 (s), 1098 (m) cm^{-1}.

*4.3.2. (R)-N-(4-chloro-1-(3-methoxyphenyl)butan-2-yl)-2,2,2-trifluoroacetamide (**6**).*

Double protected amine **5** (66 mg, 0.12 mmol) was dissolved in dry 1,2-dichloroethane (3.0 mL). Dropwise to this solution, $TiCl_4$ (40 μL, 0.365 mmol) was added, and the mixture was heated to 80 °C for 2.5 h. After cooling the mixture to room temperature, a phosphate buffer (pH 7, 10 mL, 1 M) was added. The mixture was diluted with DCM (20 mL) and the layers separated. The aqueous layer was extracted with additional DCM (2 x 10 mL). The combined organic layer was dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The residue was purified by flash chromatography (15% EtOAc in *n*-pentane) affording **6** (23 mg, 58%) as white solid. The white solid material could also be recrystallised (*n*-hexane/EtOAc) to fine crystalline needles. Data for **6**: Mp 103 - 104 °C, R_f = 0.51 (15% EtOAc in *n*-pentane). $[\alpha]_D^{23}$ −24.6 (1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.24 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.81 (app. dd, *J* 7.9, 2.4 Hz, 1H, H_{Ar}-4), 6.74 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.70 (app. s, 1H, H_{Ar}-2), 6.31 (d, *J* 7.6 Hz, 1H, NH), 4.44-4.30 (m, 1H, H-2), 3.79 (s, 3H, CH_3O), 3.56 (t, *J* 6.6 Hz, 2H, H-4), 2.97-2.83 (m, 2H, H-1), 2.17-1.95 (m, 2H, H-3). ^{13}C NMR (100 MHz): δ 160.0 (C_{Ar}-3), 156.9 (app. d, $^2J_{C,F}$ 35.7 Hz, C=O), 137.6 (C_{Ar}-1), 129.9 (C_{Ar}-5), 121.6 (C_{Ar}-6), 115.7 (q, $^1J_{C,F}$ 289.3 Hz, CF_3), 114.9 (C_{Ar}-2), 112.6 (C_{Ar}-4), 55.2 (OCH_3), 49.7 (C-2), 41.1 (C-4), 39.9 (C-1), 36.0 (C-3). IR (KBr): 3312 (m), 1704 (s), 1558 (m), 1487 (m), 1439 (m), 1262 (m), 1156 (s), 1056 (m), 699 (m) cm^{-1}.

4.3.3. (R)-tert-butyl 4-iodo-1-(3-methoxyphenyl)-butan-2-yl(2,2,2-trifluoroacetyl)carbamate (7).

The title compound was synthesized by adopting a procedure described by Saplay *et al.*[26] Tosylate **5** (136 mg, 0.249 mmol) was dissolved in acetone (2.0 mL) and added NaI (70 mg, 0.467 mmol). After vigorous stirring at 35 °C for 12 h, the solvent was removed under reduced pressure. The crude mixture was dissolved in water (10 mL) and DCM (15 mL), separated and additionally extracted with DCM (2 x 10 mL). After drying ($MgSO_4$), the solvent was removed, and the residue purified by flash chromatography (10% EtOAc in *n*-pentane). Pure iodide **7** was achieved in 78% yield as slightly yellow oil. Data for **7**: R_f = 0.65 (10% EtOAc in *n*-pentane). ^{1}H NMR (300 MHz): δ 7.19 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.80-6.72 (m, 2H, H_{Ar}-4 and H_{Ar}-6), 6.70 (app. s, 1H, H_{Ar}-2), 4.75-4.61 (m, 1H, H-2), 3.78 (s, 3H, CH_3O), 3.21-3.01 (m, 3H, H-4 and H-1), 2.91 (dd, *J* 13.7, 6.2 Hz, 1H, H-1), 2.62-2.47 (m, 1H, H-3), 2.27-2.13 (m, 1H, H-3), 1.42 (s, 9H, *t*-Bu). ^{13}C NMR (100 MHz): δ 160.2 (app. d, $^2J_{C,F}$ 44.9 Hz, **C**(=O)CF_3), 159.8 (C_{Ar}-3), 151.0 (OC(=O)N), 138.3 (C_{Ar}-1), 129.6 (C_{Ar}-5), 121.5 (C_{Ar}-6), 115.4 (q, $^1J_{C,F}$ 288.3 Hz, CF_3), 114.5 (C_{Ar}-2), 112.7 (C_{Ar}-4), 86.2 (CMe_3), 61.3 (C-2), 55.1 (CH_3O), 38.3 (C-1), 35.7 (C-3), 27.4 ((CH_3)$_3$C), 0.4 (C-4). IR (thin film, NaCl): 2984 (w), 1759 (m), 1713 (s), 1602 (m), 1586 (m), 1490 (m), 1456 (m), 1372 (m), 1260 (s), 1170 (s), 1043 (w), 836 (m) cm^{-1}

*4.3.4. (S)-2-Trifluoroacetylamino-7-methoxy-1,2,3,4-terahydronaphthalene (**8**) and (S)-2-trifluoroacetylamino-5-methoxy-1,2,3,4-terahydronaphthalene (**9**).*

The intramolecular Friedel-Crafts alkylation of chloride **6** (experiment a, Table 1, entry 4) and iodide **7** (experiment b, Table 1, entry 8) afforded partly inseparable mixtures of **8** and **9**.

(a) Table 1, entry 4: Chloride **6** (22 mg, 0.071 mmol) was dissolved in DCM (5 mL) and added $AlCl_3$ (30 mg, 0.225 mmol). The mixture was heated to 100 °C in a glass pressure tube for 20 h. The mixture was cooled to room temperature and then added an aqueous phosphate buffer (pH 7, 10 mL, 1 M) and DCM (10 mL). The layers were separated and the aqueous phase extracted with additional DCM (3 X 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. ^{1}H NMR analysis of the residue showed a product ratio **8** : **9** = 83 : 17. The crude product was purified by flash chromatography (10% EtOAc in *n*-pentane). Impure **8** (7.8 mg, 36% yield, 90% pure, >99% *ee*) was isolated as colorless crystals. The spectroscopic data of **8** was in accordance to data reported by Cecchi *et al.*[27] Enantiomeric excess was determined by chiral HPLC analysis (Chiralcel OJ, *i*-PrOH/*n*-hexane (1:9), 1.0 ml/min, 230 nm, t_R 25.4 min (*S*) and 53.8 min (*R*)). Compound **9** was purified by flash chromatography (10% EtOAc in *n*-pentane) up to 70% purity. Data for **9**: R_f = 0.42 (10% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz): δ 7.13 (app. t, *J* 8.0 Hz, 1H, H-7), 6.71 (app. d, *J* 8.0 Hz, 1H, H-6), 6.70 (app. d, *J* 8.0 Hz, 1H, H-8), 6.24 (br, 1H, NH), 4.40-4.27 (m, 1H, H-2), 3.83 (s, 3H, CH_3O), 3.17 (dd, *J* 16.2, 5.0 Hz, 1H, H-1), 2.97-2.67 (m, 3H, H-1 and H-4), 2.16-2.04 (m, 1H, H-3), 1.94-1.80 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 157.3 (C-5), 156.7 (app. d, $^2J_{C,F}$ 36.7 Hz, C=O), 134.1 (C-8a), 126.8 (C-7), 123.9 (C-4a), 121.5 (C-8), 115.8 (app. d, $^1J_{C,F}$ 288.6 Hz, CF_3), 107.7 (C-6), 55.3 (CH_3O), 45.9 (C-2), 35.0 (C-1), 27.5 (C-3), 20.7 (C-4). HRMS (ESI) calcd for $C_{13}H_{15}F_3NO_2$ $(M+H)^+$ 274.1049, found 274.1053.

(b) Table 1, entry 8: Iodide **7** (42 mg, 0.084 mmol) was dissolved in DCM (6 mL) and added $InBr_3$ (55 mg, 0.155 mmol). The mixture was heated to 80 °C in a pressure glass tube for 18 h. The mixture was cooled to room temperature and added an aqueous phosphate buffer (pH 7, 10 mL, 1 M) and DCM (10 ml). The layers were separated and the aqueous phase extracted with additional DCM (3 x 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. ^{1}H NMR analysis of the residue showed a product ratio **8** : **9** = 71 : 29. The crude product was purified by flash chromatography (10% EtOAc in *n*-pentane). Impure **8** (6.4 mg, 26% yield, 93% pure, 97% *ee*) was isolated as colorless crystals.

***4.4. Preparation and cyclization of phthalimide protected amino alcohol** 13*

*4.4.1. (R)-4-(3-methoxybenzyl)-1,3-oxazinan-2-one (**10**).*

Tosylate **4** (200 mg, 0.445 mmol) was dissolved in DMSO (10 mL) and added KOH (120 mg, 2.14 mmol). The mixture was stirred at room temperature for 18 h. An aqueous phosphate buffer solution was added (pH 7, 5 mL) to quench excess KOH, and the solvents were removed under reduced pressure. The residue was dissolved in diethyl eter (20 mL) and water (15 mL). The layers were separated and the aqueous layer extracted with additional diethyl ether (3 x 15 mL). The combined organic layer was washed with brine (15 mL) and dried ($MgSO_4$). Purification by flash chromatography (EtOAc), yielded **10** (59 mg, 60%) as a colorless crystalline material. Data for **10**: Mp 80 - 84 °C, R_f = 0.23 (EtOAc). $[\alpha]_D^{23}$ +51.6 (0.50, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.26 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.82 (app. dd, *J* 7.9, 2.5 Hz, 1H, H_{Ar}-4), 6.77 (app. d, *J* 7.6 Hz, 1H, H_{Ar}-6), 6.72 (app. s, 1H, H_{Ar}-2), 5.06 (br, 1H, NH), 4.36 (dt, *J* 11.2, 4.2 Hz, 1H, H-6), 4.22 (td, *J* 10.9, 2.8 Hz, 1H, H-6), 3.81 (s, 3H, CH_3O), 3.76-3.67 (m, 1H, H-4), 2.89 (dd, *J* 12.5, 6.9 Hz, 1H, C**H**HPh), 2.66 (dd, *J* 13.4, 8.7 Hz, 1H, CH**H**Ph), 2.09-1.98 (m, 1H, H-5), 1.86-1.74 (m, 1H, H-5). ^{13}C NMR (100 MHz): δ 160.1 (C_{Ar}-3), 153.7 (C-2), 137.5 (C_{Ar}-1), 130.1 (C_{Ar}-5), 121.4 (C_{Ar}-6), 115.1 (C_{Ar}-2), 112.4 (C_{Ar}-4), 65.5 (C-6), 55.2 (CH_3O), 52.1 (C-4), 42.9 (CH_2Ph), 27.5 (C-5). IR (KBr): 3253 (m), 2939 (m), 1699 (s), 1602 (m), 1584 (m), 1489 (m), 1434 (m), 1293 (m), 1154 (m), 1092 (m), 1043 (m), 781 (m), 736 (m) cm^{-1}. HRMS (ESI) calcd for $C_{12}H_{16}NO_3$ $(M+H)^+$ 222.1125, found 222.1130.

*4.4.2. (R)-tert-Butyl 4-hydroxy-1-(3-methoxy-phenyl)butan-2-ylcarbamate (**11**).*

The title compound was synthesized by adopting a procedure described by Ankner and Hilmersson.[28] Tosylate **4** (211 mg, 0.47 mmol) was instantaneous deprotected by the addition of a solution of SmI_2 (28 mL, 0.1 M, 2.8 mmol) in THF, water (150 mg, 8.33 mmol) and pyrrolidine (0.46 mL, 5.51 mmol), under vigorous stirring. After 5 min, diethyl ether (30 ml) and aqueous base (25 mL, 10% wt NaK tartrate + 10% wt K_2CO_3) was added. The layers were separated, and the aqueous phase was extracted with additional diethyl ether (3 x 30 mL). The combined organic layer was washed with brine (20 mL) and dried ($MgSO_4$). Purification by flash chromatography (EtOAc/*n*-pentane, 25:75 to 40:60), yielded **11** (44 mg, 32%) as a colorless oil. Data for **11**: R_f = 0.19 (20% EtOAc in *n*-pentane). ^{1}H NMR (400 MHz): δ 7.21 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.78 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-4), 6.77 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.73 (app. s, 1H, H_{Ar}-2), 4.49 (d, *J* 8.9 Hz, 1H, NH), 4.10 (m, 1H, H-2), 3.70-3.55 (m, 2H, H-4), 3.80 (s, 3H, CH_3O), 3.20 (br, 1H, OH), 2.79 (d, *J* 6.7 Hz, 2H, H-1), 1.95-1.75 (m, 1H, H-3), 1.70-1.55 (m, 1H, H-3), 1.42 (s, 9H, *t*-Bu).

4.4.3. (R)-3-Amino-4-(3-methoxyphenyl)butan-1-ol hydrochloride (12).

(a) Hydrochloride **12** was synthesized from the cyclic carbamate **10** by adopting a procedure described by Curtis *et al.*[29] Cyclic carbamate **10** (360 mg, 1.63 mmol) was dissolved in MeOH/H_2O (15 mL, 1:1) and added LiOH (320 mg, 13.4 mmol). The mixture was under vigorous stirring heated to 70 °C for 2 h. The solvent was removed under reduced pressure and the crude was dissolved in diethyl ether (30 mL) and water (15 mL). The layers were separated and the aqueous phase extracted with additional diethyl ether (4 x 20 mL). The combined organic layer was concentrated under reduced pressure. The residue was redissolved in abs ethanol (25 mL) and added conc hydrochloric acid (0.5 mL). Removal of the solvents under reduced pressure, and attempts with diethyl ether trituation, did not yield the expected solid product. However, hydrochloride **12** (244 mg, 65%) was isolated as a colorless oil and used without further purification. Data for **12**: ^{1}H NMR (400 MHz, D_2O): δ 7.37 (t, *J* 7.8 Hz, 1H, H_{Ar}-5), 7.00-6,93 (m, 2H, H_{Ar}-4, H_{Ar}-6), 6.92 (app. s, 1H, H_{Ar}-2), 3.84 (s, 3H, CH_3O), 3.80-3.59 (m, 3H, H-1 and H-3), 3.06 (dd, *J* 14.1, 6.6 Hz, 1H, H-4), 2.91 (dd, *J* 14.1, 8.0 Hz, 1H, H-4), 1.98-1.83 (m, 2H, H-2). ^{13}C NMR (100 MHz, D_2O): δ 159.9 (C_{Ar}-3), 138.1 (C_{Ar}-1), 131.0 (C_{Ar}-5), 122.9 (C_{Ar}-6), 115.7 (C_{Ar}-2), 113.6 (C_{Ar}-4), 59.0 (C-1), 56.0 (CH_3O), 52.2 (C-3), 39.0 (C-4), 34.3 (C-2). IR (KBr): 2885 (br), 1602 (m), 1489 (m), 1264 (m), 1156 (m), 1046 (s), 875 (w), 781 (s), 744 (m), 698 (s) cm^{-1}. HRMS (ESI) calcd for $C_{11}H_{18}NO_2$ (M^+) 196.1332, found 196.1335.

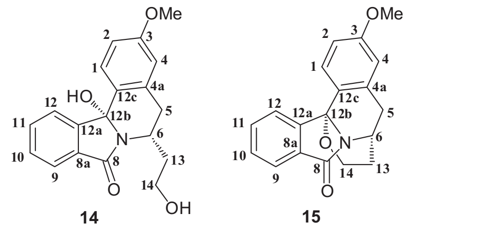
(b) Compound **12** was alternatively synthesized from *N*-Boc-alcohol **11** by adopting a procedure described by Prashad *et al.*[30] *N*-Boc-alcohol **11** (32 mg, 0.11 mmol) was dissolved in toluene (5 ml) and conc HCl (1 mL), and heated to 65 ºC for 2 hours. Evaporation of the solid under reduced pressure gave 20 mg of **12** (80% yield).

4.4.4. (R)-2-(4-hydroxy-1-(3-methoxyphenyl)-butan-2-yl)isoindoline-1,3-dione (13).

Phth protection of the amine group in **12** was performed according to a procedure described by Liu *et al.*[31] HCl-salt **12** (108 mg, 0,466 mmol) and phthalic anhydride (100 mg, 0,676 mmol) was dissolved in toluene (5 mL), and added triethylamine (70 µL, 0.502 mol). The mixture was heated to 100 °C for 18 h, then increasing the temperature to reflux, causing the majority of the solvent to distill off. Total reaction time 24 h. The crude reaction mixture was dissolved in EtOAc (30 mL), and successively washed with aqueous citric acid (10% wt, 20 mL), water (20 mL), aqueous $NaHCO_3$ (saturated, 20 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$. Purification of the crude by flash chromatography (EtOAc/*n*-pentane, 1:1) yielded **13** (65 mg, 43% yield) as a colorless oil. Data for **13**: R_f = 0.28 (EtOAc/*n*-pentane, 1:1). $[\alpha]_D^{23}$ +136.9 (1.0, CH_2Cl_2). ^{1}H NMR (400 MHz): δ 7.80-7.71 (m, 2H, Phth), 7.71-7.60 (m, 2H, Phth), 7.10 (app. t, *J* 7.9 Hz, 1H, H_{Ar}-5), 6.77 (app. d, *J* 7.9 Hz, 1H, H_{Ar}-6), 6.72 (app. s, 1H, H_{Ar}-2), 6.66 (app. dd, *J* 7.9, 2.4 Hz, 1H, H_{Ar}-4), 4.81-4.66 (m, 1H, H-2), 3.72-3.63 (m, 1H, H-4), 3.69 (s, 3H, CH_3O), 3.62-3.50 (m, 1H, H-4), 3.40 (dd, *J* 13.8, 10.0 Hz, 1H, H-1), 3.12 (dd, *J* 13.8, 6.3 Hz, 1H, H-1), 2.44-2.28 (m, 1H, H-3), 2.12-1.96 (m, 1H, H-3). ^{13}C NMR (100 MHz): δ 168.8 (Phth), 159.6 (C_{Ar}-3), 139.6 (C_{Ar}-1), 133.9 (Phth), 131.6 (Phth), 129.4 (C_{Ar}-5), 123.2 (Phth), 121.2 (C_{Ar}-6), 114.1 (C_{Ar}-2), 112.4 (C_{Ar}-4), 59.6 (C-4), 55.1 (CH_3O), 50.0 (C-2), 38.4 (C-1), 34.7 (C-3). IR (thin film, NaCl): 3460 (m), 2934 (m), 1770 (m), 1699 (s), 1602 (m), 1394 (m), 1263 (m), 1086 (m), 872 (m), 782 (m), 721 (s) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1383.

4.4.5. Preparation of diol 14 and ether 15.

Cyclization of phthalimide **13** was performed by adopting a procedure described by Harris *et al.*[16] Phthalimide **13** (22.8 mg, 0.070 mmol) was dissolved in dry chlorobenzene (1 mL) and added triflic acid (12.5 µL, 0.141 mmol). The reaction mixture was heated to 80 °C for 4 h. Quenching of the room tempered mixture was done by the addition of a phosphate buffer solution (pH 7, 10 mL, 1 M). Extraction with DCM (3 x 15 mL), drying over $MgSO_4$ and removal of the solvent under reduced pressure, resulted in a yellow crude mixture. Isolation of the two main products **14** (4.8 mg, 21% yield) and **15** (2.3 mg, 11% yield), both colorless oils, was performed by column chromatography (5% MeOH in DCM).



14 **15**

Fig. 4. Numbering of **14** and **15** with respect to ^{1}H and ^{13}C NMR interpretation.

Data for **14**: R_f = 0.31 (5% MeOH in DCM). ^{1}H NMR (400 MHz): δ 7.88 (app. d, *J* 7.7 Hz, 1H, H-12), 7.61-7.55 (m, 1H, H-11), 7.54 (d, *J* 8.7 Hz, 1H, H-1), 7.40-7.31 (m, 2H, H-9 and H-10), 6.74 (dd, *J* 8.7, 2.6 Hz, 1H, H-2), 6.64 (d, *J* 2.6 Hz, 1H, H-4), 5.27 (s, 1H, 12b-OH), 4.69-4.60 (m, 1H, H-6), 3.87-3.64 (m, 2H, H-14), 3.77 (s, 3H, CH_3O), 3.05 (dd, *J* 15.8, 6.5 Hz, 1H, H-5), 2.88 (dd, *J* 15.8, 5.2 Hz, 1H, H-5), 2.29-2.11 (m, 1H, H-13), 1.94-1.78 (m, 1H, H-13). ^{13}C NMR (100 MHz): δ 168.4 (C=O), 159.5 (C-3), 147.8 (12a), 135.3 (4a), 132.3 (C-11), 130.4 (8a), 129.2 (C-10), 128.5 (12c), 127.7 (C-1), 123.2 (C-9), 123.0 (C-12), 113.9 (C-4), 112.5 (C-2), 87.1 (C-12b), 68.9 (C-14), 55.3 (CH_3O), 46.5 (C-6), 34.7 (C-5), 34.3 (C-13). Absolute configuration (6*R*, 12b*S*) was determined by NOESY analysis. IR (KBr): 3403 (m), 1682 (s), 1610 (m), 1467 (m), 1389 (m), 1256 (m), 1111 (m), 1035 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{20}NO_4$ $(M+H)^+$ 326.1387, found 326.1395.

Data for **15**: R_f = 0.48 (5% MeOH in DCM). ^{1}H NMR (400 MHz): δ 8.02 (app. d, *J* 7.4 Hz, 1H, H-12), 7.87 (app. d, *J* 7.4 Hz, 1H, H-9), 7.69 (d, *J* 8.5 Hz, 1H, H-1), 7.65 (app. t, *J* 7.4 Hz, 1H, H-11), 7.55 (app. t, *J* 7.4 Hz, 1H, H-10), 6.81 (dd, *J* 8.5, 2.7 Hz, 1H, H-2), 6.72 (d, *J* 2.7 Hz, 1H, H-4), 4.99 (app. t, *J* 5.4 Hz, 1H, H-6), 3.85-3.79 (m, 2H, H-14), 3.80 (s, 3H, CH_3O), 3.51 (dd, *J* 17.2, 6.8 Hz, 1H, H-5), 2.95 (d, *J* 17.2 Hz, 1H, H-5), 2.32-2.17 (m, 1H, H-13), 1.69 (app. d, *J* 12.0 Hz, 1H, H-13). ^{13}C NMR (100 MHz): δ 166.9 (C=O), 159.6 (C-3), 144.9 (12a), 138.7 (4a), 131.6 (C-11), 130.4 (8a), 129.8 (C-10), 128.0 (C-1), 124.6 (12c), 124.1 (C-9), 123.3 (C-12), 112.8 (C-4), 112.8 (C-2), 85.3 (C-12b), 59.2 (C-14), 55.3 (CH_3O), 41.6 (C-6), 34.4 (C-5), 31.1 (C-13). Absolute configuration (6*R*, 12b*S*) was determined by NOESY analysis. IR (KBr): 3442 (w), 2919 (m), 1781 (s), 1607 (m), 1429 (m), 1244 (m), 1036 (m) cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ $(M+H)^+$ 308.1281, found 308.1292.

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Paper III

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